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A Normative Perspective of the American Opioid Public Health Epidemic: Regulatory Lessons to Portugal

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Contents

PART II

Abstract

In response to the opioid epidemic, which has claimed approximately 700,000 lives, a national public health emergency was declared in the United States in 2017. The epidemic was triggered by medical overprescription under the influence of marketing strategies crafted to convince physicians pain was being poorly treated and that fear of addiction was unwarranted.

This study describes the origins of the epidemic through a normative perspective and verifies similarities and differences between regulations from Portugal and the United States. The aim is to raise awareness of potential contributors to an opioid epidemic in Portugal.

With this purpose, scientific literature and American and Portuguese regulations were reviewed. A qualitative study with semi-structured interviews of Portuguese key-informants within the field of pain management was conducted to address their views and perceptions of opioid use in Portugal.

Medical caution with opioid use was withdrawn and a new practice of treating chronic pain unrelated to cancer with opioids was consensually approved without adequate empiric evidence. Direct-to-consumer marketing, unregulated sales representatives visits and gifts and donations to physicians may have contributed to the conception of the epidemic.

In Portugal, direct-to-consumer marketing is limited and physician-industry relations are strictly regulated, nonetheless, opioid use for chronic pain has been approved by legislation and opioid sales have increased by 54-fold since 2001. Key-informants agree opioid efficacy is limited and preventive measures for opioid overprescription, namely, pain management medical education, systematic monitoring of opioid dispensing, and information to patients are indicated.

Key-words: Opioids, epidemic, regulations, chronic pain, direct-to-consumer marketing

Resumo

Em resposta à epidemia de opióides foi declarada uma emergência nacional de saúde pública nos Estados Unidos em 2017. A epidemia foi desencadeada por excesso de prescrição médica e estratégias de *marketing* criadas para convencer os médicos de que a dor estava a ser sub-tratada e que o medo da adição era injustificado.

Este estudo descreve as origens da epidemia sob uma perspetiva regulamentar dos Estados Unidos, verificando semelhanças e diferenças com a situação portuguesa. O objetivo é consciencializar para prevenir a possibilidade de uma epidemia similar em Portugal.

Foram analisadas literatura bem como regulamentação americana e portuguesa. Foi realizado um estudo qualitativo com entrevistas semi-estruturadas a informantes-chave portugueses, especialistas em tratamento da dor, com o objetivo de abordar as suas perceções sobre o uso de opióides em Portugal.

A cautela médica com os opióides foi abandonada e o seu uso para tratar dor crónica não-oncológica consensualmente aprovado mesmo sem evidência suficiente. Do ponto de vista normativo, visitas de representantes de vendas, *marketing* direto ao consumidor e doações a médicos podem ter contribuído para a conceção da epidemia.

Em Portugal, o marketing direto ao consumidor é restrito e as relações entre médicos e indústria são estritamente regulamentadas. No entanto, desde que o uso de opioides para dor crónica foi aprovado em 2001 as vendas destes medicamentos aumentaram 54 vezes.

Os informantes-chave concordam que a eficácia do opióide é limitada e medidas preventivas para o excesso de prescrição são indicadas, nomeadamente, educação especializada, monitoramento e informação ao doente.

Palavras-chave: opióides, epidemia, regulamentos, dor crónica, marketing direto ao consumidor

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Foreword

Four milligrams of intravenous hydromorphone every four hours, a potent opioid known by the brand name Dilaudid, was prescribed by the attending physician during morning rounds on a summer day in New York City. The year was 2006, and the patient was a young black man with sickle cell trait, not the disease. Knowingly, sickle cell disease causes serious medical problems such as stroke, blindness, and painful bone infarct. Sickle cell trait, on the other hand, is a mutation present in one of two alleles, only causing serious health problems rarely, and within the context of severe dehydration. This fact did not seem to hold any clinical relevance to the attending physician who felt strongly the patient's pain should be treated aggressively. The perplexed patient could not hide his amazement to the treatment plan, to which he exclaimed: "I didn't know this dosage was possible"! The matter of fact was that neither did I.

It was in this opioid permissive scenario that I completed an internal medicine internship, neurology residency and neuro-oncology fellowship in the United States between 2006 and 2012. The rhetoric *du jour* was that opioid was safe for treatment of any pain and that failing to treat pain was in flagrant violation of the hippocratic oath. Physicians were retrained to believe that being overly cautious about prescribing opioids was a sign of ineptitude. Educated physicians were not expected to be afraid of opioids' adverse effects. In those days, recommending opioids as the treatment of last resort was no longer best practice.

I did not know then I was witnessing, first hand, the workings of the most deadly drug epidemic of American history. I am visited every so often by the memories of emergency department consultations for young caucasian women with refractory migraine. On one occasion, after days of vigorous treatment with several non-opioid medications, the patient desperately asked, "When are you giving me the real medicine?". I was stunned, mostly because it took me so long to notice the underlying problem.

This dissertation is dedicated to the opioid epidemic that unraveled before my eyes. It is an investigative review that patches together what prompted its birth. It is also a warning to other countries that indiscriminate use of opioids is not safe and that the cost of neglecting this fact is too high.

Abbreviations

AAMP - American Academy of Pain Medicine

al. - line (*alínea*)

AMA - American Medical Association

APED - *Associação Portuguesa para o Estudo da Dor*

APS - American Pain Society

art. - article (*artigo*)

CDC - Centers for Disease Control and Prevention

CFR - Code of Federal Regulation

CMS - Centers for Medicare and Medicaid Services

DEA - Drug Enforcement Administration

DGS - *Direção-Geral da Saúde*

EMCDDA - The European Monitoring Centre for Drugs and Drug Addiction

FDA - Food and Drug Administration

FDCA - Federal Food, Drug, and Cosmetic Act

FSMB - Federation of State Medical Boards

HHS - United States Department of Health and Human Services

JC - Joint Commission

REMS - Risk Evaluation and Mitigation Strategy Program

SUPPORT - Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment

USC - United States Code

List of Figures

INTRODUCTION

Background

In response to the opioid epidemic that plagues the United States, President Trump declared a public health emergency on October 16, 2017 (HHS, 2017). A public health emergency is declared when an acute threat to the health of a significant number of people is acknowledged (WHO, 2008). The declaration allows for regulatory changes to be made by public agencies and for the investment of financial and human resources (WHO, 2008). It is estimated that over 700,000 people died since 1999 of opioid use overdose (CDC, 2018a).

The epidemic was triggered by medical overprescription of opioids, a practice set in motion after the Food and Drug Administration (FDA) approval of Oxycontin, the brand for a medication with the active ingredient oxycodone, a long-acting opioid, in 1995 (deShazo *et al*., 2018; Kolodny *et al*., 2015; Jones *et al*., 2018; Vadivelu *et al*., 2018, Bonnie, Ford, & Phillips, 2017). Oxycontin was marketed as safe, non-addictive, and effective, despite the lack of scientific evidence for any of these claims (Von Korff *et al*., 2011; Franklin, 2014).

In that same year, the American Pain Society (APS) launched the campaign "5th Vital Sign" that established pain should be monitored as closely and frequently as blood pressure, heart rate, body temperature and respiratory rate (Campbell, 1996). Furthermore, APS indicated that pain, independently from the etiology and duration, could be safely treated with opioids (Campbell, 1996).

The standardisation of opioid use for pain unrelated to cancer have resulted in considerable morbidity and mortality associated with the misuse of prescription opioids (deShazo *et al*., 2018; Kolodny *et al*., 2015; Jones *et al*., 2018; Vadivelu *et al*., 2018, Bonnie, Ford, & Phillips, 2017; Franklin, 2014).

To halt the epidemic, new Federal and State regulations restricting medical prescription of opioids were enacted. In addition, the FDA issued a special report with recommendations, and, in 2016, the Center for Disease Control and Prevention (CDC) crafted a new guideline for opioid use (Dowell, Haegerich & Chou, 2016). The resultant emergence of opioid use disorder and the ensuing stricter regulations increased the levels of illicit heroin and fentanyl use provoking new waves of opioid related epidemics (CDC, 2018a).

The Fifth Vital Sign campaign reached the Portuguese regulatory framework in 2003 by advocacy of the National Plan Against Pain's commission. In accord with the American campaign, it was established by the *Direção-Geral da Saúde* (DGS), the Portuguese public agency responsible for health policies, that the measurement of level of pain should be included in the patient's vital signs sheet (*Direcção-Geral da Saúde*, 2003).

In 2008, the DGS released new best practices clinical guidelines permitting the use of opioids for pain unrelated to cancer, despite the lack of adequate scientific evidence (*Direcção-Geral da Saúde*, 2008b).

Following the new guidelines, oxycodone was approved by *Infarmed*, the Portuguese public agency analog to the FDA, in 2011, and, in 2016, increased subsidy by the government for prescription of strong opioids to treat chronic pain unrelated to cancer was approved (*Direcção-Geral da Saúde*, 2013; Ordinance nº 329/2016 December, 20). Consequently, the use of medical opioids has increased by 70% between 2012 and 2017 (Reis, 2017). However, this data does not distinguish between treatment for pain related or unrelated to cancer.

The public health epidemic born in the United States was a result of a myriad of events that when observed through a normative lens can be summarised by either permissive or violated regulatory framework ruling this topic. When both Purdue Pharma and APS filed for bankruptcy in 2019, after indictment with criminal charges, it became clear fraud played an important part in this tragedy. This dissertation, however, proposes to

describe the regulatory framework that allowed for the epidemic outbreak rather than delve into matters of corruption.

The study attempts to indicate normative analogy between American and Portuguese regulatory frameworks in order to increase awareness of its strengths and weaknesses with regard to opioid use, sales, and marketing.

Objectives and Scope

The dissertation's primary objective is to study the origins of the American opioid epidemic through a normative perspective and verify similarities and differences to Portuguese regulations for opioid use, sales and marketing, with special regard to opioid use for pain unrelated to cancer. The purpose is to raise awareness of possible normative weaknesses that could contribute to the emergence of an opioid epidemic in Portugal as the one observed in the United States. In order to fulfil this objective the following secondary objectives were sought:

1. Describe the context, factors, and outcomes of the American opioid epidemic;
2. Identify and describe the regulations for medical use of opioid valid at the outbreak of the epidemic in the United States and ensuing regulatory counter-measures;
3. Identify and describe regulations for medical use of opioid in Portugal;
4. Explore key informants' perceptions about opioid medical use and regulatory control in Portugal.

The American public health emergency opioid epidemic is the subject matter of this dissertation and the identification of the factors that allowed for the epidemic's outbreak is the starting point to the investigation. A normative perspective is used to describe and analyse the documented culprits for the epidemic. The dissertation does not hypothesise about unpublished potential culprits nor claims to address every possible one.

In broad terms, the scope of this study embraces several topics that could each result in independent research within the context of opioid history, epidemiology, public health law and policies. In specific terms, the study considers laws and regulations on marketing and sales of opioids, restrictions to medical prescription of opioids, pharmacovigilance procedures and medical guidelines for opioid use in the United States and in Portugal.

Although some state statutes will be cited, the study is restricted to the description of specific federal statutes concerned with opioid use, sales and marketing, therefore, not every legal instrument in force and not every law and regulation to that matter. It addresses public health and law *lato sensu* and does not intend to be by any means a legal study. This dissertation has a multidisciplinary approach oriented in its essence to public health promotion and prevention.

Structure

The dissertation begins with the description of background, objectives and scope, structure, and methods. It is further divided in two parts: Part I with preliminary concepts, epidemiological traits of the epidemic, identified causes for the epidemic, and pertinent regulations ruling opioid medical use and sales. Part I ends with an overview of opioid use in Portugal and analog regulations for its medical use and sales.

Part II documents the field work performed for this research; a qualitative study with key-informants within the field of pain medicine, Portuguese medical regulatory frameworks, and opioid addiction. Key-informants were interviewed to discuss their views on opioid medical use, sales, and regulations and its similarities and differences to the American practice. Methods, results and discussion for the qualitative study are described in detail on Chapter 6. The final conclusions of this dissertation are discussed on Chapter 7.

Methods

In order to achieve these objectives, a review, dating back to 1995 and onwards, of book chapters, academic articles, medical guidelines, American federal and state regulations, Portuguese statutes and guidelines, public hearings, and news media articles, was conducted. Pubmed, Scielo, Google Scholar, Web of Science, Jstor, B-on were the scientific databases used for the research. A personal visit to the *Biblioteca Nacional de Portugal* was accomplished to ensure a thorough search of published doctoral and master studies specific to the use of opioids in Portugal.

For data regarding the medical opioid use in Portugal, a formal request for data concerning the sales of strong opioids was placed to *Infarmed.* The total number of packages of morphine, buprenorphine, hydromorphone, fentanyl, oxycodone, oxycodone with naloxone and tapentadol sold over the past 20 years, yearly, was provided by *Infarmed* to the author. This data is described in the text and graphs produced by the author on Chapter 5.3.

After a thorough revision of the epidemic's causes and major developments a descriptive review of components of the federal health law effective at the origin of the epidemic in the United States was pursued. The same aspects of the American regulations were compared to Portuguese rules alike. The study's design does not permit any conclusion of causation between the laws and the epidemic, instead, it raises hypotheses for possible culprits or facilitators. References and citations followed the Harvard referencing style.

PART I

Chapter 1. Preliminary Concepts

This chapter is dedicated to the description of the types of opioids, the history of its use in the United States, and the new terminologies implicated within the broad term of opioid use disorder. This chapter also provides a summarised review of the definition, importance, and research activities of public health law.

1.1 Opium, Opiates and Opioids

Opium is an extract of the plant opium poppy, *Papaver somniferum*, used to treat pain in ancient Mesopotamia by Assyrians, Greeks, and Sumerians. (The Editors of Encyclopaedia Britannica, 2018a). The extract is composed of organic compounds such as morphine, codeine and thebaine (*ibid*). Analgesics that contain natural derivatives of opium are referred to as opiates.

With the advent of synthetic drugs that act as opium derivatives, a wider term gained scientific relevance: opioid. Opioids include any substance, natural, synthetic or semi-synthetic, endogenous or exogenous, agonist or antagonist, that carry affinity with opioid receptors in the central nervous system. (Ciarallo, 2011).

Opioids are deemed strong or weak based on its potency for relieving pain; stronger opioids have higher propensity for misuse and addiction (Koob & Le Moal, 2005). Examples of strong opioids are morphine, hydromorphone, hydrocodone, oxycodone, fentanyl and methadone. Codeine is considered a weak opioid, as well as tramadol when given in lower dosages. Heroin is a strong opioid derived from morphine, no longer manufactured for medical use.

Codeine and morphine are natural opioids, and hydromorphone, hydrocodone, oxycodone are semi-synthetic opioids, or drugs with similar chemical structure to opium (*ibid*). Different from natural and semi-synthetic, synthetic opioids are fully developed in laboratory, namely, fentanyl, methadone and tramadol, among others.

Today, opioids are used in palliative care to treat moderate to severe pain and alleviate discomfort and respiratory distress in the dying. Besides the feeling of well being elicited by some opioids, side effects such as pruritus, constipation, respiratory depression, nausea and vomiting, as well as physical dependence and addiction are hallmarks of this class of medication.

The text will address more frequently the opioids protagonists of the public health crisis: the medically prescribed oxycodone and hydrocodone, and less so the illegally distributed fentanyl and heroin. The use of methadone, a long acting opioid, used predominantly for treatment of opioid dependence, will not be addressed.

1.2 History of Opioids in America

Since the American Revolution (1775-1783), opium has circulated American streets to relieve the pain of British wounded soldiers (Trickely, 2018). In 1803, morphine was isolated from opium by the German scientist Friedrich Sertuner and, in its pure form, was found to be ten times more potent. With the advent of the hypodermic needle in 1853, morphine was used to treat pain and other ailments with unprecedented success (Courtwright, 2001). It was used profusely during the American civil war (1861-1865) and resulted in approximately 100,000 soldiers addicted to opium (Carroll, 2016).

Still in the nineteenth century, smoking opium rather than injecting it was introduced in the West coast by Chinese immigrants; addicted to opium themselves as a result of the Opium Wars waged by British colonialists in China (1839-1860) (Trickely, 2018). Chinese immigrants, following the hope and promises provided by the Gold Rush

(1848-1855), brought to California opium dens; rooms where people could smoke opium.

The idea of morphine as a relief-all medication transported the demographics of morphine use from soldiers to women seeking help to treat menstrual pain and neurosis (Courtwright, 2001). By the end of the nineteenth century, physicians were picking up on the dangers of morphine addiction and medical journals would frequently offer warnings about it (*ibid*).

The opioid market was essentially unregulated until the creation of heroin, a derivative of morphine distributed under the premise it would be a safer substitute to morphine. Heroin was sold by the company Bayer to treat excessive cough and pain (Trickely, 2018). The practice was slowly picked up by physicians as a dangerous one and as the number of prescriptions were already trending down a delayed legislative reform arrived in 1914 with the enactment of the Harrison Narcotics Tax Act (Courtwright, 2015). The act's goal was to end non-medical use: opium-based drugs were no longer sold over-the-counter and record-keeping of sales and dispensing were obligatory (*ibid*). A complete ban of manufacture and sales of heroin arrived in 1924 with the Anti-Heroin Act.

Post-World War II America was marked by a heroin epidemic affecting predominantly black communities in urban suburbs. Government action, not only directed towards opioids, but also cocaine and crack use, began during the Nixon administration under the slogan "War on Drugs" (1971) (The Editors of Encyclopaedia Britannica, 2018b). The effort resulted in the creation of the Drug Enforcement Agency (DEA), an agency dedicated to the consolidation of intelligence to fight illegal drug trade and use, and monitor medical distribution. The campaign reached momentum during the Reagan years with greater allocation of resources and the slogan launched by the first-lady Nancy Reagan:"Just Say No" (1984), aimed at children in school (The Editors of Encyclopaedia Britannica, 2018b). Illegal drug use was considered a criminal offence, hence, resources were directed to incarceration and punishment rather than treatment for

addiction. As a result, the number for imprisonment increased from 50,000 to 400,000 between 1980 and 1997 (*ibid*).

This dissertation describes how lessons learned by physicians during the nineteenth century were discarded under the solace of expert opinion with the term "opiophobia", the medical jargon to delegitimise caution exerted on past experiences. This new opioid epidemic emerged with legal medical prescriptions and approval of regulatory public agencies, once again with the promise of a less addictive opioid.

1.3 Opioid Use Disorder: Concepts and Vocabulary

The opioid epidemic prompted revision of the language used to classify substance use disorders with the intent of mitigating the effects of stigma worsened by the use of pejorative language (National Academies of Sciences, Engineering, and Medicine, 2017). Hence, as of the new edition of the *Diagnostic and Statistical of Mental Disorders* launched in 2013, *abuse*, an expression no longer current, has been substituted by the more encompassing term: *substance use disorder*, or, in this particular case, *opioid use disorder* (APA, 2013).

Opioid use disorder involves other terminologies: *addiction*, *dependence*, *tolerance*, and *misuse*. Addiction refers to the brain pathology that affects neuronal pathways responsible for the control of behaviour, cravings, and the pursuit of reward; dependence indicates the presence of withdrawal symptoms without fulfilling the dysfunctional psychosocial factors that characterises addiction (ASAM, 2011). Unlike addiction and dependence, tolerance designates the growing need for larger doses of the drug to achieve its intended effect. The term misuse is reserved to the inadequate use of prescribed medication, such as, taking the medication more frequently than indicated or for reasons other than the one prescribed. Misuse is a behaviour that precedes addiction and is part of the criteria that defines opioid use disorder (*ibid*). In addition to this constellation of terminologies, the definition of opioid use disorder also includes social isolation, inability to fulfil obligations, the increasing dominance of the substance over

the person's life, and incapacity to stop using the drug despite negative physical, emotional, and social consequences (APA, 2013).

As a result of medical overprescribing of opioids, redundant amounts of unused pills were available in people's homes (CDC, 2018; HHS, 2016; Theisen, *et al.* 2018). The use of these pills by friends and family members who have not been prescribed the medication is called *non-medical opioid use*. Furthermore, the expression *diversion* is used to describe the sale of medically prescribed pills in the illegal markets (National Academies of Sciences, Engineering, and Medicine, 2017).

1.4 Public Health Law: Definition and Scope

Public health is the field concerned with the actions required to protect and promote the health of a given population. In 1988, Acheson defined public health as "the art and science of preventing disease, prolonging life and promoting health through the organized efforts of society" (Acheson, 1988: para.1). The responsibility of ensuring welfare and health falls into the government's duties invested by the people's power, when in a democratic state, under the solace of the rule of law (Gostin, 2007).

The rule of law establishes that a normative framework composed of laws, regulations and public policies shall guide the government's execution of its duties and powers (*ibid*).

Normative frameworks are composed of legally binding instruments such as executive orders, decrees, statutes, court's sentences, and non-binding instruments such as best practices guidelines and technical standards (World Health Organization, 2017). The mainstay difference is that a legally binding instrument is obligatory, hence, if not respected, sanctions normally apply. Non-binding legal instruments, expressed often in the form of recommendations or resolutions, are essentially guidelines and non-mandatory norms lacking direct sanction when not observed.

In the United States, federal, state, and local governments have jurisdiction to enact public health laws (Gostin, 2007). Public health law and policy are influenced by government agencies and many areas of civil society, such as education institutions, the media, and the private sector (Institute of Medicine, 2011). These sources provide for the delimitation of the scope of public health laws. According to Gostin (2007) public health law is defined as:

> "… the study of the legal powers and duties of the state to assure the conditions for people to be healthy (e.g., to identify, prevent, and ameliorate risks to health in the population), and the limitations on the power of the state to constrain the autonomy, privacy, liberty, proprietary, or other legally protected interests of individuals for protection or promotion of community health." (p.3)

Public health law, henceforth, must address the tension between protecting society and the individual, sometimes in detriment to the individual's fundamental rights. This conflict is evident when the court must decide on, for example, whether to restrict liberty and order quarantine, limit privacy and oblige disease notification to a vulnerable partner, and limit autonomy by mandating vaccination (Chichevalieva, 2011).

Still according to Gostin (2007), public health law attends to the correspondence between the state and the population, as well as between the state and an individual who offers risk to the aforementioned population. Furthermore, it relies on evidence-based scientific methods, and is empowered to exert proportional coercion in the name of collective welfare (*ibid*).

As a tool to advance the promotion of public health, public health law has made important achievements; among them smoking bans, safety-belt-use laws, fluoridation of community water supplies, regulation of food and prescription drugs, and regulation of workplace safety practices are some worth noting (Goodman *et al*., 2006).

In order to verify the impact of law on health, public health law research studies the outcomes of legal practices on population health (Burris, 2017). From lawmaking to intervention, legal practices, and changes in behavior and environment, public health law research aims to measure, monitor, and determine correlation between law and health effects (*ibid*).

Chapter 2. The Opioid Epidemic

The American opioid epidemic has claimed approximately 700,000 lives between 1999 and 2017 (CDC, 2018a). It is estimated that more than 90 individuals perish daily due to opioid overdose (HHS, 2017). In 2017, a nationwide public health emergency, referred to as the opioid crisis, was acknowledged by the American government (*ibid*).

According to the CDC (2018a), the epidemic is now understood as a continuum of three overlapping waves beginning with licitly prescribed opioids followed by two waves of illicit opioid use: heroin and fentanyl. The first wave, caused by overly prescribed opioid medication for the treatment of chronic pain began in the late 90s (*ibid*). The second and third waves, triggered in 2010 and 2013, respectively, were prompted by the rigorous control of opioid prescription in response to the first wave and the resultant increase search for illicit cheaper opioids by those who had developed opioid use disorder (HHS, 2016).

In this chapter, an overview of the epidemic will be described with attention to the epidemic's demographics, geographic distribution and the supervening social consequences. The effects of parental drug use on newborns and children will be reported, as well as the disruption of the American family and the saturation of the foster care system.

A brief summary of what is known at this point about the risk factors for addiction will be discussed with special attention to the risk factors induced by the liberalisation of opioid use to treat pain unrelated to cancer.

The chapter ends with an analysis of the epidemic's financial burden, the diverse sources of expenses and the different proposed estimates of the total cost.

2.1 Overview

The United States is home to over 300 million people of which 60.4% declare themselves non-hispanic white (U.S. Department of Commerce, 2018). It is estimated 50 million people are affected by chronic pain, and among those 40% report limitations on daily activities secondary to pain (CDC, 2018b). In 2016, 48.5 million individuals older than 12 years misused prescription opioids or used illicit heroin (*ibid*). The ensuing result was 63,600 deaths from drug overdose in 2016 and 72,000 in 2017 of which more than 60% were attributed to opioids (Stoicea *et al*., 2019; Hedegaard, Warner, & Miniño, 2017). Approximately 130 Americans die daily due to opioid overdose, more than 20 times the number of deaths due to alcohol poisoning, estimated at 6 per day (Scholl *et al.*, 2018, Kenny *et al.*, 2015). In a poll performed in 2015, 56% of Americans declared encountering someone with opioid use disorder; either who took opioid for non-medical use, was addicted, or died from opioid overdose (DiJulio *et al*., 2015).

Opioid consumption in the United States has increased over the past two decades. In 2009, Americans consumed over 80% of semisynthetic opioids produced in the world, namely, oxycodone and hydrocodone (Hauser *et al*., 2016). In the span of seven years, between 2006 and 2012, 76 billion opioid pills were distributed by several pharmaceutical companies, most of which are currently being prosecuted for failure to report opioid sales to the DEA; this represents on average 248 pills per person in the U.S. (Higham, Horwitz & Rich, 2019).

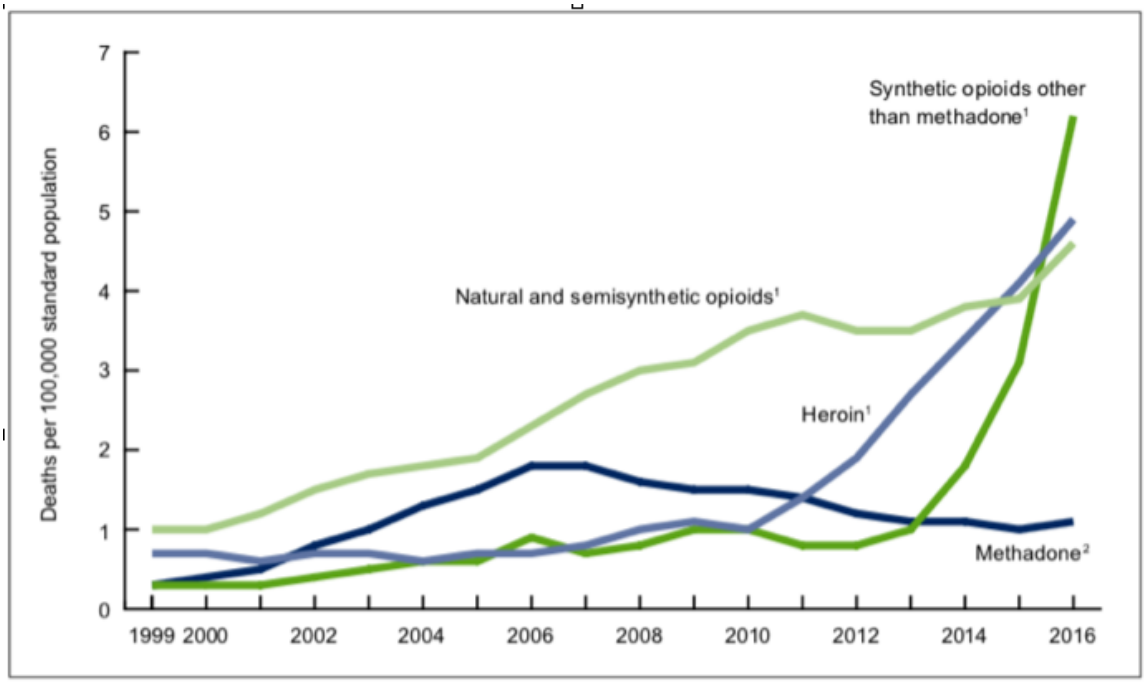
Over 13 million Americans with private health insurance, aged 18 to 64 years, were prescribed opioids for pain unrelated to cancer in 2009 (Liu *et al*., 2013). Of those, 59% were women with a mean age of 43.2 years; one-third of patients had 3 or more opioid prescriptions and 12% received prescriptions with more than 90 days supply (*ibid*). In a different study, conducted in 2010, 1.38 million people enrolled to Medicaid (a public insurance for those claiming limited income) were treated with opioids: 74% were

women, 45.9% of opioid recipients were aged 18-34 years, and 53% received 3 or more prescriptions in a year (Mack *et al*., 2015).

The rate of fatal drug overdose associated with opioids has increased over time. In 1999, the age-adjusted rate, measure that removes the effect of age for comparison, associated with prescription opioids, was 1.4 per 100,000, by 2011 the rate climbed to 5.4, and by 2016 a downturn to 4.4 was observed (Figure 1: Hedegaard, Warner, & Miniño, 2017:p. 4). Following the same upward curve but with later onset, the age-adjusted rate overdose due to heroin increased from 0.7 in 1999, to 4.9 in 2016, and for fentanyl analogs, also referred to as synthetic opioids other than methadone, the rate went from 0.3 in 1999 to 6.2 in 2016 (*ibid*). Between 2013 and 2016 overdose deaths secondary to fentanyl increased by 100% every year, climbing from 1,919 to 18,335 (Ducharme, 2018).

Federal preliminary data indicates a slight decline at the rate of overdose deaths due to opioids during 2018, suggesting the epidemic may have reached its peak and control measures are working to some extent (Ducharme, 2019).

Figure 1. Age-adjusted drug overdose death rates, by opioid category: United States, 1999–2016 (Hedegaard, Warner, & Miniño, 2017:p.4)



2.2 Demographic Pattern

In 2015, nobel prize winners in Economic Sciences, Anne Case and Angus Deaton, published an article that identified a downturn in the life expectancy of white non-hispanic Americans (Case & Deaton, 2015). The research revealed that if yearly mortality rate for whites, aged 45-54, had decreased as expected and as observed in other developed countries, five hundred thousand deaths would have been prevented between 1999 and 2013 (Figure 2: Case & Deaton, 2015:p.15079). Parallel to the increased mortality, the authors observed increased rates of suicide, poisoning, and requests for social security insurance for disability (Figure 3: *ibid*). This observation corroborated with the indiscriminate use of opioid medications noted within the past two and a half decades.

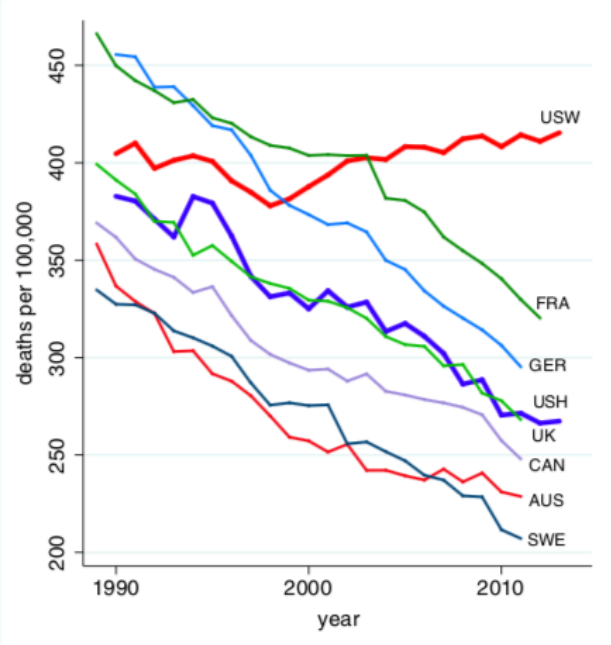


Figure 2. All-cause mortality, ages 45–54 for US White non-Hispanics (USW), US Hispanics (USH), and six comparison countries: France (FRA), Germany (GER), the United Kingdom (UK), Canada (CAN), Australia (AUS), and Sweden (SWE).
(Case & Deaton, 2015:p.15079)

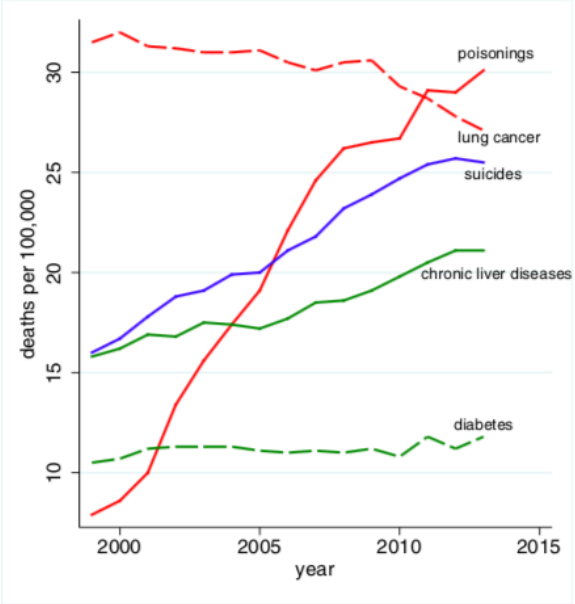
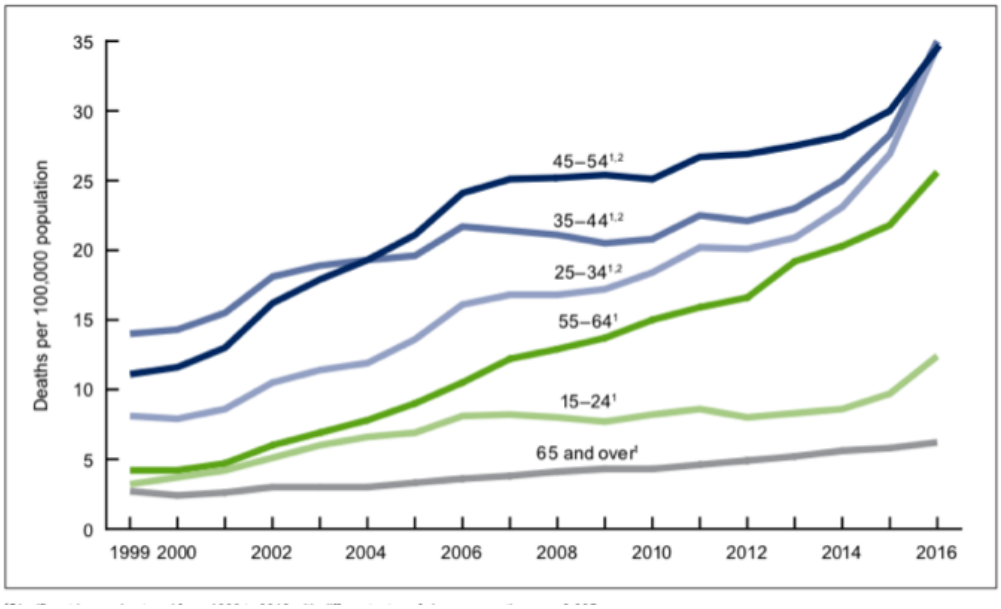


Figure 3. Mortality by cause, white non-Hispanics ages 45–54. (Case & Deaton, 2015:p.15079)

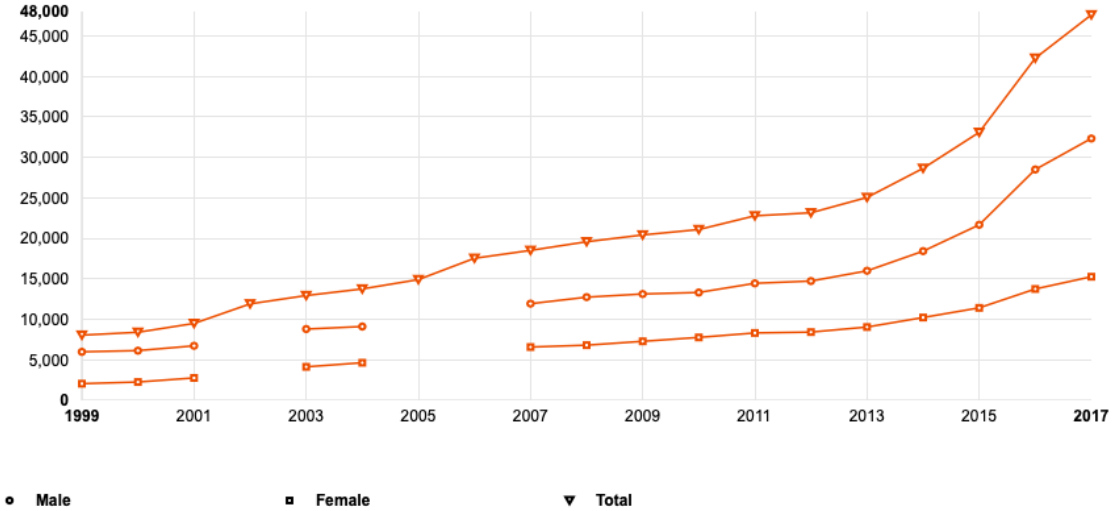
Although the increased mortality was more pronounced among those aged 45-54, a similar trend was observed in all age groups between 30 and 54 years (Case & Deaton, 2015). By 2011, overdose death rates among those aged 15 to 44 years reached the same level as the age group 45-54 years (Figure 4: Chen, Hedegaard & Warner 2014: p.2). The rate of deaths due to prescription opioids increased by 8.2% for those aged 25-34 years, 6.2% for the 35-44 age group and 4.9% for the 55-64 age group between 2014 and 2015 (Rudd *et al*., 2016). These same age groups demonstrated fatal overdose rate reduction due to prescription opioids between 2016 and 2017 (Scholl *et al*., 2018). This improved trend was offset by the increase in overdose deaths due to illicit manufactured fentanyl which registered an average ranging from 36 to 50%, affecting all age groups (*ibid*).

Figure 4. Drug overdose death rates, by selected age group: United States, 1999-2011 (Chen, Hedegaard & Warner 2014: p.2)



The epidemic has affected both men and women, but overdose death rates have been significantly higher in men (Chen, Hedegaard & Warner 2014: p.1), (Figure 5) (KFF, 2017a).

Figure 5. Opioid Overdose Deaths by Gender in the United States: Timeframe 1999-2017 (KFF, 2017a)



As the epidemic unfurled from prescription opioids to heroin and illicitly manufactured fentanyl, a distinctive pattern of unintentional drug overdose mortality taking into account age, race, and gender was observed by Jalal *et al*., (2018). Deaths related to heroin and fentanyl analogs cluster in groups of younger white men living in urban surroundings, while overdose deaths due to prescription opioids, in decline since 2016, prevail among older white women living in rural areas (*ibid*). Similarly, Mosher *et al*., (2017: p.926) observed hospitalisations due to heroin overdose were more prevalent in urban areas, while prescription opioid overdose hospitalisations were higher in rural and small urban areas (Figures 6 and 7). In both the urban and rural settings, most individuals admitted to the hospital were white: 75-84% urban and 90.13% rural (*ibid*).

Figure 6. Prescription opioid overdose hospital admission trend by rurality, 2007 - 2014 (Mosher et al., 2017:p.926)

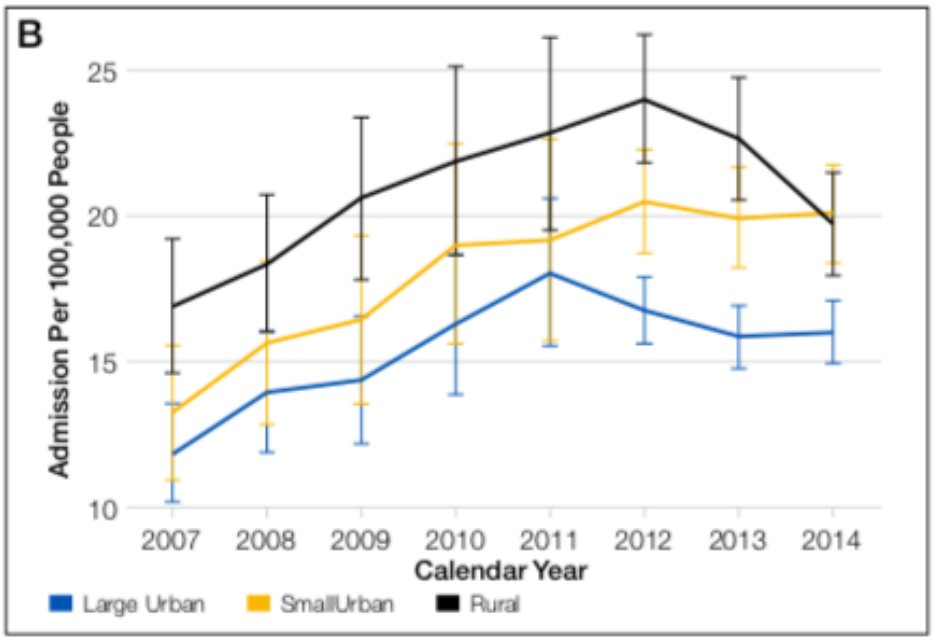
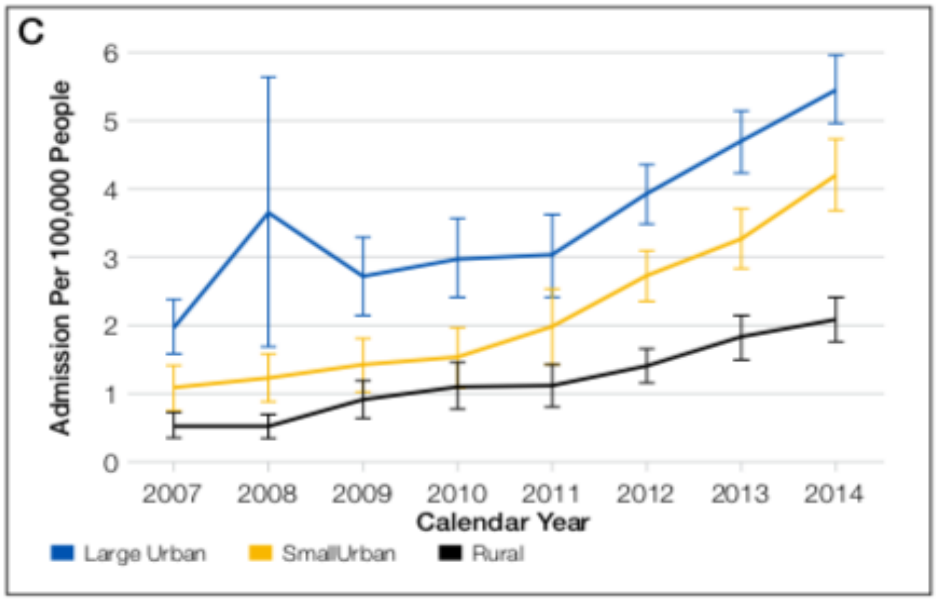
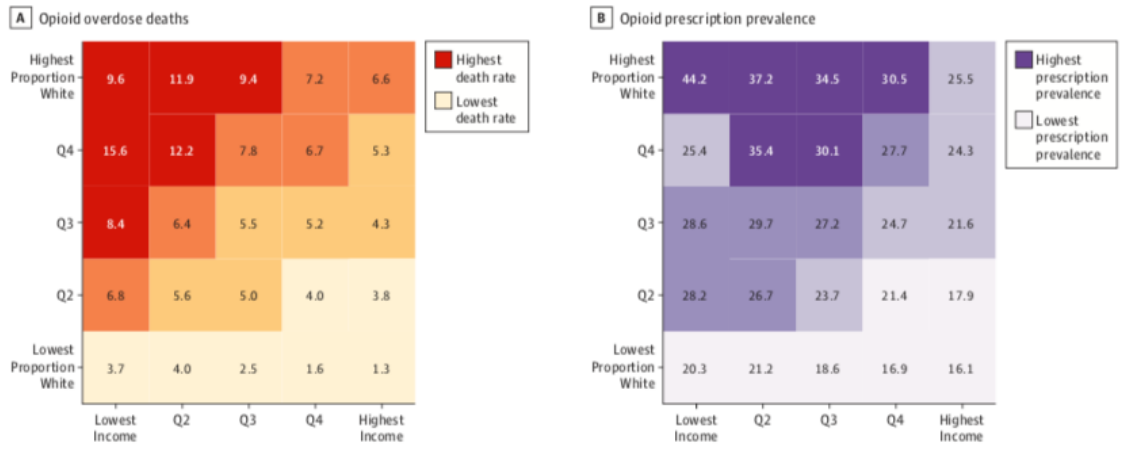


Figure 7. Heroin overdose hospital admission trend by rurality, 2007 - 2014 (Mosher et al., 2017:p.926)



The opioid epidemic has affected predominantly non-hispanic white Americans (Figure 8: KFF, 2017b). White patients had better insurance coverage and were more likely to receive an opioid prescription from their physician (Hansen & Netherland, 2016). During the epidemic's first wave, the number of deaths among white Americans increased from 5,669 in 1999 to 17,927 in 2010 while among blacks and hispanics it ranged between 868 and 1380 during the same period (KFF, 2017b). From 2011 onwards, with the increased availability of illicit heroin and fentanyl, cheaper options when compared to the pharmaceutical opioids, mortality rates from opioid overdose increased for all races: 48% for whites, 59% for hispanics, and 73% for blacks (*ibid*). Still, in 2017, mortality among whites far exceeded blacks: 37,113 compared to 5,513, respectively (*ibid*).

Figure 8. Opioid Overdose Deaths by Race/Ethnicity in the United States: Timeframe 1999-2017 (KFF, 2017b)



A, Annual age-standardized opioid overdose death rates per 100 000 people. B, Annual prevalence of receiving at least 1 prescription for an opioid among individuals 15 years or older. Both figures represent the entire state of California, showing quartiles of mean annual rates during the 2011 through 2015 study period. The y-axis represents the percentage of individuals in each zip code tabulation area identifying as non-Hispanic white, by quintiles (Qs). The x-axis represents quintiles of the mean per capita annual income at the zip code tabulation area level. Values for all 25 quintile-quintile pairs are shown with color and text.

Medical racial bias is assumed to stem from diverse misguided beliefs: blacks and whites are biologically different, minorities are more prone to substance abuse, and black people are less sensitive to pain (Santoro *et al*., 2018). In a study involving 6,170 emergency department visits between 2006 and 2010, minorities were at least 22% less likely to receive treatment for pain, including opioids (Brigham and Women's Hospital, 2015). In California, a study showed association between opioid overdose and number of prescriptions in which both were concentrated in whites with low-income (Friedman et al., 2019).

On the one hand, this discrepancy protected black people and other minorities from the opioid epidemic, on the other it revealed medical treatment disparities based on race (*ibid*). Furthermore, Friedman *et al.*, (2019) point out the first wave of this epidemic is atypical, for it affects the majority group rather than the minority, commonly the most susceptible group.

2.3 Geographic Distribution: Regions and States

The United States is home to fifty states and five main regions: West, Midwest, Northeast, Southwest, and Southeast (National Geographic, 2019: Figure 9). An increase in fatal overdose due to prescription opioids was initially observed in the Southwestern and Appalachian regions (Jalal *et al.*, 2018). The Appalachian region encompasses the states along the Appalachian Mountains (Figure 10: ARC, 2019). It stretches from southern New York to northern Mississippi harbouring the rural state of West Virginia and parts of other 12 states including, Ohio, Maryland, Tennessee, and Kentucky. This region is home to counties with the lowest household income in the country severely affected by all three waves of the epidemic (*ibid*).

Figure 9. Map of the United States' Regions and States (National Geographic, 2019)

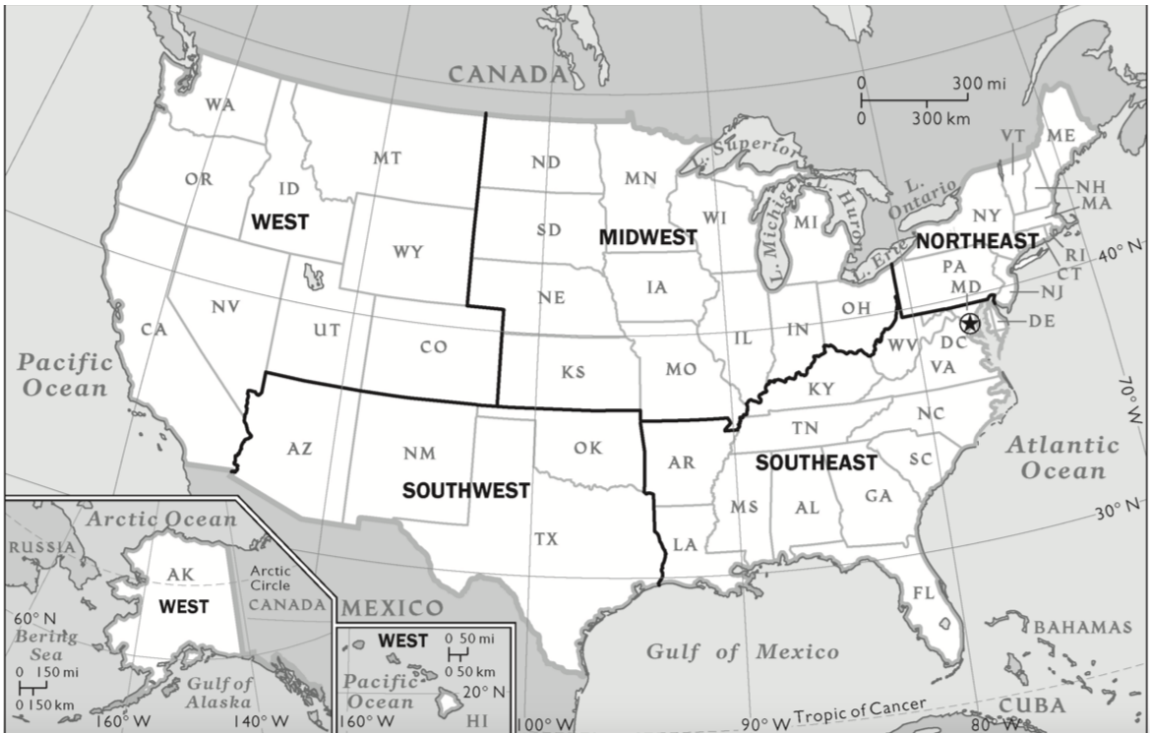
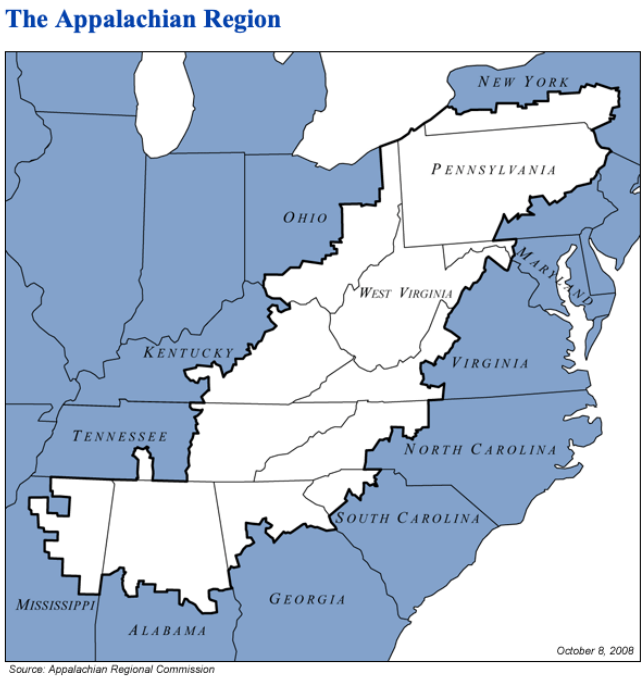


Figure 10. Map of the Appalachian Region (ARC, 2019)



The epidemic initially expanded to states surrounding Appalachia and to the West region, coming to spare no region or state as the epidemic spread (Jalal *et al.*, 2018). During the epidemic's first wave, prescription-opioid-overdose hospital admissions rose steadily from 2000 to 2011 in all regions, albeit more pronounced in the South and the Midwest; from 2010 onwards, heroin-opioid-overdose hospitalisation climbed in all regions, but most remarkably in the Northeast and the Midwest (Unick & Ciccarone, 2017).

Throughout the epidemic West Virginia endured the highest rate of overdose deaths and received the highest concentration of pills per person calculated at 66.5 (Higham, Horwitz & Rich, 2019). In 2006, the majority of fatal overdoses were attributed to non-medical use and diversion of the prescription opioids (Hall *et al.*, 2008). Ten years later, it remains the state with the highest rate of death for all opioids combined as well as for illicit manufactured fentanyl in isolation (Scholl *et al.*, 2019). Along with West Virginia, the states of Kentucky, South Carolina, Tennessee, and Nevada received the highest number of pills per person, ranging from 63.3 to 54.7 (Higham, Horwitz & Rich, 2019).

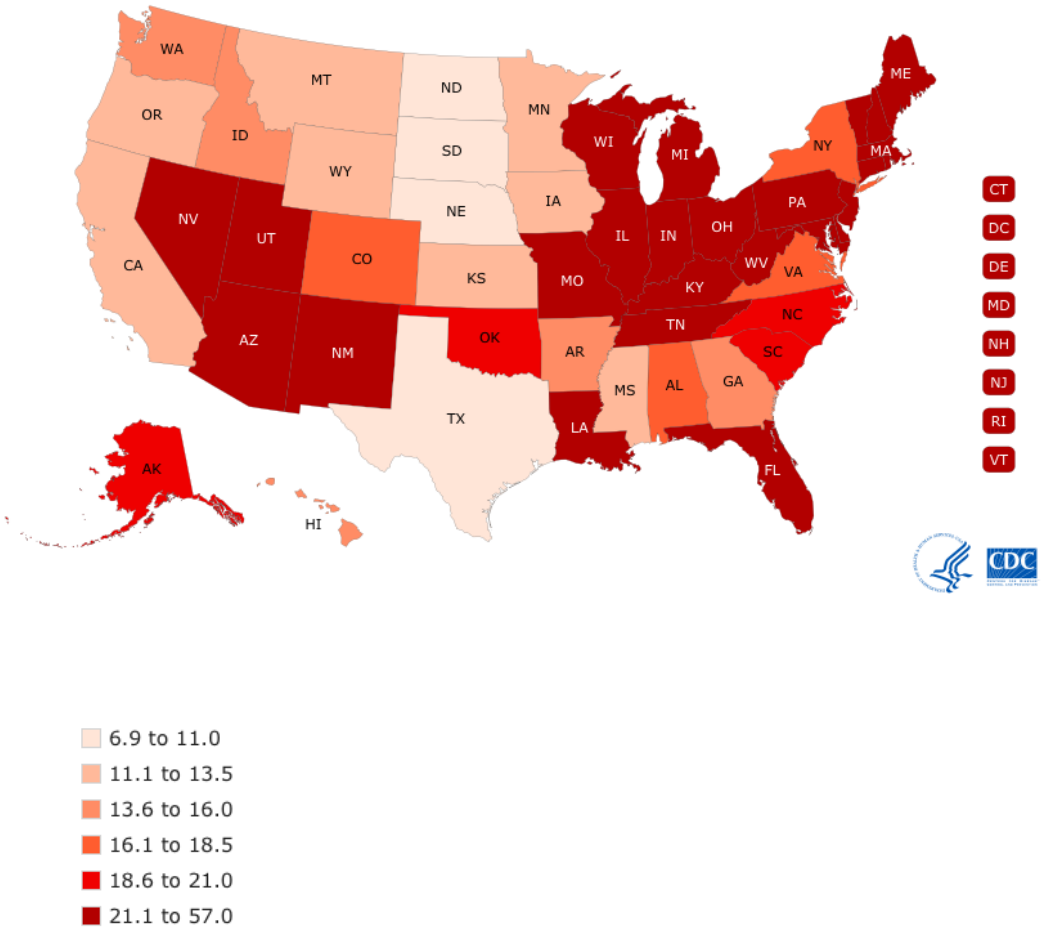
Rural areas within these states concentrated an even higher number of pills per person, as high as 306 in Norton, Va. (*ibid*).

By 2016, the states of Virginia, Alaska, Arizona, Florida, Maryland, Massachusetts, Pennsylvania, and South Carolina had utilised their legal authority to declare the opioid epidemic a public health emergency. In Virginia, on average 3 people died and 24 nonfatal overdoses were treated daily in 2016; Massachusetts registered 5 overdose deaths per day in 2017 (Macy, 2018). Bostonians were encouraged to carry naloxone (the drug that reverses opioid effects) in their backpacks (*ibid*). To make it ubiquitous it is no longer required to have a prescription to purchase naloxone, which costs on average $50 dollars.

The transition of prescribed opioid to illicit fentanyl has altered the geographic distribution of the epidemic to some extent. Fentanyl-induced overdose hotspots mirror spots previously concentrated with prescription opioids but is moving towards larger metropolitan areas, while heroin, commonly prevalent in urban areas, has found its way into smaller counties (Jalal *et al.*, 2018). With the advent of the heroin and illicit manufactured fentanyl sub-epidemic, emergency department visits for opioid overdose increased in all 5 regions: 69.7% in the Midwest, 40.3% in the West, 21.3% in the Northeast, 20.2% in the Southwest, and 14% in the Southeast (Vivolo *et al.*, 2018).

In 2017, the top five states with the highest rate of fatal overdose were West Virginia, Ohio, Pennsylvania, District of Columbia, and Kentucky; age-adjusted rate of drug overdose deaths ranged between 57,8 to 37.2 per 100,000 population, and the number of deaths ranged from 5,388 in Pennsylvania to 310 in the District of Columbia (Figure 11: CDC, 2019).

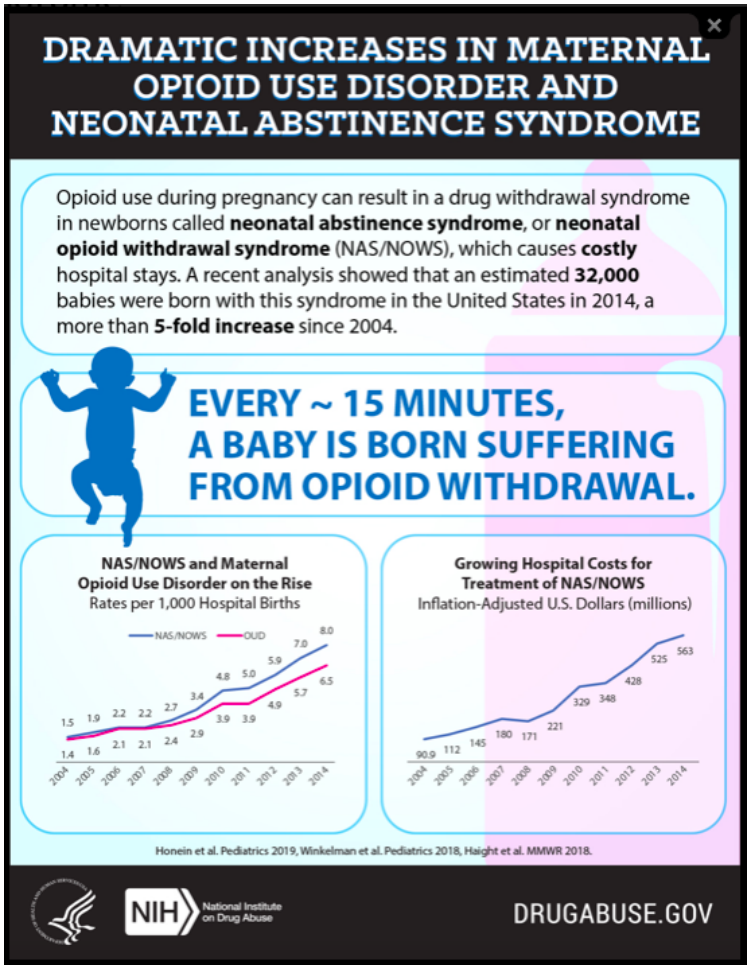
Figure 11. Age-adjusted rates of drug overdose deaths by state, US 2017 (CDC, 2019)



2.4 Effects on Newborn and Children

The incidence of opioid use disorder in women at reproductive-age has been climbing steadily resulting in a surge of pregnant women with opioid use disorder, prenatal opioid exposure, and neonatal abstinence syndrome (Figure 12: NIDA, 2019). Neonatal abstinence syndrome due to opioid withdrawal is a treatable condition which may present with excessive crying, fever, sweating, vomiting, rapid breathing, among others. Labor among mothers with opioid use disorder have increased by more than four times between 1999 and 2014 (*ibid*). As a result, 32,000 infants are born yearly with neonatal abstinence syndrome, the equivalent of 1 for every 15 minutes (*ibid*; Haight et al. 2018).

Figure 12. Maternal Opioid Use Disorder and Neonatal Abstinence Syndrome (NIDA, 2019)



Consonant with the established association of opioid use disorder and low-income, the proportion of infants delivered with neonatal abstinence is greater among mothers covered by Medicaid: 73.7% in 2004 and 82% in 2014 (Winkelman *et al.* 2018). The incidence of neonatal abstinence syndrome increased from 2.8 per 1000 births to 14.4 per 1000 births within the 10 year-timeframe among mothers covered by Medicaid (*ibid*).

Prenatal opioid exposed children develop lower cognitive function compared to non-exposed children (Nygaard, 2015). The onset of discrepant cognitive scores occurs later in girls when compared to boys, suggesting the consequences of opioid exposure during pregnancy have lasting effects (*ibid*).

Notwithstanding the biological consequences of opioid exposure in infants and children, problems within the social domains of life are also taking place. As a result of parental drug abuse, children are being removed from their parent's care by social workers (Radel *et al*., 2018). Increase in the opioid prescription rate was associated with a 32% rise of foster children in Florida (Quast, Storch, & Yampolskaya, 2018). Nationwide, a 10% increase of children in foster care due to neglect or death have occurred between 2012 and 2016, according to the U.S. Department of Health & Human Services (Radel *et al.*, 2018). This estimate does not account for orphaned children who are now living with their grandparents or other family members.

2.5 Risk Factors for Opioid Use Disorder

Risk factors for addiction are multifactorial. Research studies have indicated genetic predisposition is a contributor to the development of opioid use disorder, as well as for response to treatment of drug addiction (Kreek *et al.*, 2012). Genetic variability is compounded by environmental factors in the social domain, such as educational level, family support, level of income, and peer influence (*ibid*; Blanco & Volkow, 2019). Additionally, individuals with mental health disorders, especially with anxiety and mood disorders, are at higher risk of developing opioid use disorder (Edlund *et al.,* 2014; Armaghani *et al.*, 2014).

The opioid epidemic, however, was marked by the unverified medical practice of recommending opioid use for the treatment of chronic pain unrelated to cancer (Franklin, 2014). This new medical practice created the growth in demand for opioid therapy that was accompanied by a large-scale supply (Bohnert & Ilgen, 2019). The new balance of supply and demand of opioids increased the percentage of the population exposed to this class of medication for a longer duration allowing for new avenues of research into the science of addiction.

According to a systematic review, rates of addiction among those with chronic pain was found to range between 8-12%, and misuse between 21-29%, (Vowles *et al.,* 2015). Several studies emerged trying to identify risk factors of opioid misuse among those treated for chronic pain unrelated to cancer.

A prospective cohort study involving veterans with median age of 52 years demonstrated the duration of opioid use to be a risk factor for new-onset non-medical use of prescription opioids (Barry *et al.,* 2018). The chances of non-medical use increased when opioids were prescribed for 30 to 180 days and for more than 180 days at 1.65 and 2 times the adjusted hazard ratio, respectively, when compared to less than 30 days prescription (*ibid*).

The same observation was verified in Oregon, where 5% of 536,767 new opioid users, excluding cancer patients, became long-term users in the follow-up year of the study (Deyo *et al.,* 2017). Number of refills, higher dosage, and long-acting opioids were risk factors for transitioning to long-term use, defined as six or more opioid prescriptions over the following year (*ibid*).

Similarly, patients treated with opioids for pain unrelated to cancer had a significantly increased odds of developing opioid use disorder when duration of treatment exceeded 90 days and when the dosages were higher (Edlund *et al.,* 2014). In comparison to those not prescribed opioids, chronic use of opioid with low-dosages had an odds ratio of 14.92 for developing opioid use disorder, while those using high-dose opioids chronically had an odds ratio of 206 (*ibid*).

Kaiser Permanente, an American integrated managed care consortium, created an opioid registry to identify patients at risk of developing opioid use disorder in Northern California. In the span of 4 years, among approximately 400,000 insured patients, 2.7% developed opioid misuse and 1,044 had an overdose (Campbell *et al.,* 2018). Younger age, concomitant benzodiazepine use, psychiatric comorbidities, higher dosages, and prolonged use were identified as risk factors for opioid use disorder (*ibid*).

In the surgical setting, the treatment for acute pain unrelated to cancer with opioids has unleashed yet another cohort of patients with opioid use disorder (Theisen *et al.,* 2018). In a cross-sectional study with longitudinal outcome, chronic opioid use was observed in 18% of opioid-naive patients who received opioids for pain treatment after major spine surgery (Dunn *et al.,* 2018). In those exposed to opioids prior to surgery the prevalence of opioid use was above 50% at 12 months (*ibid*). In a cohort involving over 1 million patients who underwent surgery, 56% received an opioid prescription post-operatively; of those, 0.6% were found to have new ICD codes of opioid misuse documented in their medical charts (Brat *et al.,* 2018). The rate of misuse increased with each additional refill by 44% (*ibid*).

Prescription opioids misuse are a risk factor for heroin use; 80% of new heroin users reported non medical use of prescription opioids in the past 12 months (Muhuri, Gfroerer & Davies, 2013). Between 2002-2011 approximately 3.6% of those misusing prescription opioids reported transition to heroin (*ibid*). The common pathway for the transition to heroin use began with taking prescribed opioids as medically indicated but thereafter followed by tolerance, misuse, dependence, and opioid withdrawal symptoms (Bonnie, Ford & Phillips, 2017).

Importantly, the rate of addiction and the relevance of long-term opioid therapy as a risk factor may be underestimated by the retrospective nature of most studies dedicated to answer this question and by the short duration of follow-up (Busse *et al.*, 2018, Voon, Karamouzian & Kerr, 2017). A longitudinal prospective study spanning several years has not been performed to date, and therefore, the rate of development of addiction in the long-term is unknown (Voon, Karamouzian & Kerr, 2017).

2.6 The Epidemic's Economic Cost

Research dedicated to quantify the economic burden of the opioid epidemic has divided the costs into three main areas of expenses: medical care, criminal justice and reduced productivity (Birnbaum *et al.*, 2011). In 2007, the total cost of the epidemic was approximately $55.7 billion, this estimate has risen to $78.5 in 2013 (*ibid*; Florence et al., 2016).

Medical care costs which include treatment and medical prescription, as well as research expenses and preventive programs accounted for $25 billion in 2007 and $28.9 in 2013 (Birnbaum *et al.*, 2011; Florence *et al.*, 2016). In 2014 alone, it is estimated $563 million dollars were required to cover medicaid costs for the treatment of neonatal abstinence syndrome (NIDA, 2019). Approximately $760 million were spent to support the bloating foster care system (Radel *et al.*, 2018). Diminished labor force productivity resulted in a $25 billion loss and criminal justice costs, which derive from police

services, litigations, correctional facilities and property theft summed up to $5.1 billion (Birnbaum *et al.*, 2011).

In a different analysis, Segel *et al.* (2019) measured the loss in tax revenue due to the reduction of the labor force. To their calculation, between the years of 2000 and 2016, the state and federal governments failed to collect $11.8 and $26 billion income tax revenue, respectively, due to the diminishing workforce (*ibid*).

The Council of Economic Advisors of the Executive office of the President of the United States used, yet, a different metric to measure the epidemic's economic cost. One which considers the value of life beyond the estimated earnings lost with death, the Value of a Statistical Life: the calculation of how much the individual is willing to spend to avoid mortality risk factors (The Council of Economic Advisors, 2017). Taking into account 33,091 deaths due to opioid overdose, most of them aged between 25 and 55 years old, and an incremental 24%, estimated to be the amount underreported every year, the estimated cost of the opioid epidemic was $431.7 billion, in 2015 (*ibid*). The council's estimate is more than five-fold higher than the ones reported in previous studies. This discrepancy is justified by the different measurements used, the increase in overdose deaths along the years, the inclusion of heroin attributed deaths, and the accountability of the underreported overdose deaths (*ibid*).

The different cost estimates reflect the difficulty in accounting for the multiple layers and sources of financial burden cast by the epidemic on public institutions and American families. In summary, an epidemic that began within a predominantly rural, white, low-income population has spread to all strata of society and the full social, economic, and emotional costs are still unraveling.

Chapter 3. Contributing Factors to the Opioid Epidemic

The origins of the current opioid epidemic have been the subject of ample academic publications. Four main causes are consensually reported: a concerted movement by pharmaceutical industry and medical associations to address the undertreatment of pain, increase in medical marketing investment, fraudulent practices by pharmaceutical industries, and a slow response to action by public institutions (deShazo *et al.*, 2018; Kolodny *et al*., 2015; Jones *et al*., 2018; Vadivelu *et al.*, 2018, Bonnie, Ford, & Phillips, 2017). This chapter will address each of these causes in some detail.

This chapter will describe the efforts of pain specialists to enhance pain treatment and liberalize opioid use through the "pain as the fifth vital sign campaign". The strategy employed by Purdue Pharma to enhance opioid sales is described. To understand the American normative framework with regard to medicinal products, the FDA's duties and the federal regulations that enforce medical advertisement, drug approval, labelling, and pharmacovigilance is reviewed.

This chapter will highlight the regulatory weaknesses, modifications, and violations, potentially responsible for facilitating the spread of the epidemic. According to a position paper by the American Academy of Neurology, the importance of the regulatory changes in the 90s allowing for the permissive use of opioid, and the endorsement of long-term opioid use for chronic pain unrelated to cancer, a medical practice previously considered too risky for misuse and addiction, contributed to the epidemic (Franklin, 2014). Other authors point to the regulations that determine the oversight of marketing and promotion of drugs as the important culprit (Van Zee, 2009, Psaty & Merril, 2017; Bonnie, Ford, & Phillips, 2017).

Importantly, this analysis does not intend to exhaust all potential contributors to the opioid epidemic, and it does not address every regulation pertinent to its conception. It is an overview of the main pointed causes responsible for the genesis of the opioid

epidemic and the correspondent normative structure that has been either violated or inadequate to prevent it.

3.1 *The Fifth Vital Sign Campaign*

In 1995, the APS in partnership with the American Academy of Pain Medicine (AAMP), professional membership organisations, launched the campaign, "Pain as the Fifth Vital Sign" dedicated to address a perceived consensus among pain specialists that pain was being inadequately treated. The Presidential Address, by the sitting president Dr. James N. Campbell, laid out the campaign's premises and goals to improve pain management.

Part of the plan was to adopt a bedside pain evaluation. The evaluation of pain would rely on self-reported pain rating scales, numerical, visual, or verbal, which prompted the patient to rate the pain between 0 and 10, 0 meaning no pain and 10 the worst pain. Nurses should document self-reported pain ratings along with the other vital signs, namely, heart rate, blood pressure, respiratory rate, and temperature. In his address, Dr. Campbell defended the distinction between chronic and acute pain, and cancer and non-cancer pain were ambiguous and deleterious for appropriate pain management (Campbell, 1996). The statement that followed endorsed the use of opioids for chronic pain unrelated to cancer based on the clinical experience of the use of opioids in cancer patients who lived longer than expected and derived long-term pain relief (*ibid*). Physician's cautiousness was decried as secondary to misinformation and regulatory control:

> 'Misinformation about what addiction is and myths about liability for addiction in patients with pain have not been the only reasons for underuse. Fear of regulatory reproach by government is certainly another source of concern' (Campbell, 1996: p.87).

Ultimately, the campaign mitigated opioid's adverse side effects by claiming addiction is rare, tolerance uncommon, respiratory depression short-lived, and the risk of diversion should not be offset by the benefit of relieving pain of those who suffer (Von Korff *et al.*, 2011).

In order to remove the barriers for treatment of chronic pain unrelated to cancer and opioid use, the APS unraveled a list of actions: the creation of a foundation funded by the industry to serve the public, the assembly of an advocacy group for legislation reforms, and the development of an APS Clinical Practice Guidelines Committee to mandate treatment reimbursement by government institutions (Campbell, 1996).

3.1.1 Legislation and Quality Measures Shift Medical Practice

The concerted effort by APS prompted legislative reform in 1999 when California's legislature passed Assembly Bill 791, which added to the Health and Safety Code that pain should be documented in the chart along with the other vital signs; other states followed (Baker, 2017). Additionally, on October 31, 2000, the U.S. Congress passed a resolution establishing the "Decade of Pain Control and Research". In 1999 the Veteran's Health Administration, a public health institution dedicated to the provision of care for American war veterans, embraced the fifth vital sign campaign providing it with added legitimacy nationwide.

In 2000, the Joint Commission[1] (JC), a non-profit organisation responsible for the accreditation of healthcare organisations and programs in the United States and internationally, adopted the campaign and instituted new quality standards for pain evaluation. Healthcare facilities were now obliged to assess pain regularly to maintain accreditation (Tompkins *et al.*, 2017).

In order to guarantee federal healthcare fund reimbursements it is necessary to achieve the JC parameters of standard of care or the federal agency's Centers for Medicare and

[1] Previously known as Joint Accreditation Hospital Commission or JAHCO

Medicaid Services (CMS), responsible for administering the funds for healthcare for the aged and the poor respectively. The CMS used a patient satisfaction survey, part of a larger survey, the Hospital Consumer Assessment of Healthcare Providers and Systems, to simplify and calculate reimbursements for medical providers (CMS, 2019a). The survey is one of the items used by the Hospital Value-Based Purchasing program, a program dedicated to the improvement of patient safety through measurement of quality of care rather than quantity of services provided (CMS, 2019b). The hospitals receive their payments based on several quality measures of performance included in the survey. Between 2006 and 2016, the assessment of patient satisfaction related to pain management was one of the items used to define federal reward bonuses (Adams, Bledsoe, & Armstrong, 2016). The Fifth Vital Sign campaign premise was inserted into the intricate healthcare evaluation process and became a determinant factor for financial reimbursement.

Early evaluations in the setting of acute postoperative pain control showed that higher doses of morphine were prescribed between 2000-2002 and the increased use of opioids in that setting did not result in higher rates of increased length of stay, naloxone use, or nausea (Frasco *et al.*, 2005). However, questions surrounding the safety of numerical scales guiding pain treatment emerged in 2005 when Villa *et al.* (2005) disclosed the incidence of opioid oversedation increased from 11 to 24.5 per 100,000 patients along with sentinel events of fatal respiratory depression. A decade after the launch of the Fifth Vital Sign campaign, the cost of patient satisfaction was measured by the study of Fenton *et al*. (2012), composed of a prospective cohort of 51,946 respondents to the national Medical Expenditure Panel Survey between 2000-2007. The results indicated that highest patient satisfaction scores were associated with an increase in hospital admissions, higher prescription drug expenditures, and increased mortality (*ibid*).

Once embraced by the JC and the CMS, hospital's caution with abiding to the campaign's guidelines could translate into less federal reimbursement, an apprehension only abated by diligent respect to the newly instated requirements. While measuring pain as a fifth vital sign became an obligation in many states once enacted by legislative

bodies, the recommendations made by APS were non-binding, and, therefore, did not oblige physicians to treat pain with opioids. Indirectly, however, it pushed hospitals to train the physicians and nurses to be more aggressive with pain treatment and made it easier and less concerning for physicians to prescribe opioids in the inpatient and outpatient setting.

By 2009, the JC acknowledged the relationship between numerical pain scale and opioid addiction prompting removal of the statement that pain should be assessed in all patients, and in 2011 reiterated that other strategies for pain relief despite opioid addiction should be sought (Baker, 2017). In November 2016, the CMS ruled that the pain management survey be removed from the scoring system used by the Hospital Value-Based Purchasing Program (CMS, 2016). In 2018, a new type of survey dedicated to pain communication rather than management was approved (Thompson, 2017).

Along with the JC and the CMS, other medical associations that had previously embraced the fifth vital sign campaign have withdrawn their support. Current efforts to improve pain management and treatment are directed to the refinement of the unidimensional aspect of the pain scale to a multidimensional type that includes assessment of function debilitated by pain as well as psychosocial risk factors that might alter self-reporting levels of pain (Baker, 2017).

The Fifth Vital Sign campaign's changes to the medical practice of pain treatment and the opioid use were twofold: instituted a simplistic but systematic pain assessment that prompted aggressive treatment with opioids for hospitalised patients and endorsed the empirically unproved treatment of chronic pain unrelated to cancer with opioids based on expert consensus alone.

3.1.2 FSMB, DEA, and Opioid Prescription

Parallel to the efforts drawn to measure pain frequently and to treat it with opioids, advocacy groups, medical associations and pharmaceutical companies, succeeded in softening the guidelines and regulations of medical prescription for opioids under the supervision of the DEA and the Federation of State Medical Boards (FSMB), a non-profit organisation that assists state medical boards with licensing and regulatory overview of physicians (Franklin, 2014).

Signed into law in 1971, the Controlled Substances Act is the federal statute that determines the regulation of production, distribution, and possession of drugs with risk for abuse (Controlled Substances Act Title 21 Ch. 13 §811). The act classifies five different schedules of drugs based on its potential for abuse; *schedule I* drugs have the highest potential and *schedule V* the lowest. *Schedule I* drugs are not indicated for medical use in any circumstance and schedule II drugs are allowed with major restrictions. Drugs classified between *schedule III* and *schedule V* are accepted for medical use. Most opioids are considered *schedule II* drugs, the exceptions being heroin, a *schedule I* drug, and buprenorphine and low-dose codeine derivatives, *schedule III*.

In 1973, the DEA was created to enforce the Controlled Substance Act (*supra* 1.2). The DEA's duties include, among others, fighting illegal drug trade and monitoring illegal sales of licit drugs. To that end physicians, pharmacists, and other healthcare professionals must request a licensing number to prescribe or sell controlled substances. By this mechanism, the DEA monitors the amount of controlled substances prescribed by healthcare professionals.

Both federal and state legislative bodies are authorised to regulate the use of controlled substances (Hill, 1996). The comprehension of the regulations is muddled by the heterogeneous policies advocated by the different state medical boards (*ibid*). A survey conducted by the APS in the early nineties revealed physicians refrained from

prescribing opioids for chronic pain management due to fear of regulatory control (Turk & Brody, 1992). Some states requested specialist consultation for patients with substance abuse problems in need of treatment with opioids, while others indicated the necessity of chart documentation that alternate treatment methods were attempted prior to opioid use (Joranson *et al*., 2002).

In order to create consensus and mitigate the policies' heterogeneity, eleven workshops about pain management, attended by nation-wide state board members, were sponsored by the FSMB and the Pain Policy Study Group, a research program at the University of Wisconsin that received funding from Purdue Pharma (*infra* 3.2). The workshop's educational material included debunking the "exaggerated fear of addiction and concerns about regulatory scrutiny" (Joranson *et al*., 2002:p.140).

In 1998, the FSMB developed the "Model Guidelines for the Use of Controlled substances for the Treatment of Pain" (*ibid*). The Model, a non-legally binding instrument, was endorsed by the DEA to reassure physicians that regulatory control over the amount of opioid prescribed would allow for appropriate access to those in pain (*ibid*). The goal was to create a uniform pain management policy among medical state boards.

The model's goal was to quell physician's fear of regulatory sanctions while prescribing opioids by allowing unlimited number of prescriptions (Franklin, 2014). The Model's policies were adopted by several states and, henceforth, regulatory changes loosening the restrictions for opioid prescriptions were embedded into legislature (*ibid*). For example, in 1999, Washington State's administrative code, a legally binding instrument, stated: "No disciplinary action will be taken against a practitioner based solely on the quantity and/or frequency of opioids prescribed" (Franklin *et al.,* 2015:p.464).

FSMB guidelines, along with the aforementioned changes into Washington State's administrative codes have since changed and been updated to reflect a more conservative use of opioids (*ibid*).

A concerted action taken by advocacy groups, medical associations, pain management experts, and the industry resulted in recommendations and laws that changed the landscape of pain evaluation and management. A permissive opioid scenario was created and persisted for a few years before step-by-step, both legislative and non-legislative instruments were reviewed in order to halt the epidemic (*infra* 4.2).

3.2 Purdue Pharma's Marketing Strategy

The opioid epidemic has direct ties to the pharmaceutical industry and medical associations fostered by the unprecedented investment in professional marketing (Van Zee, 2009; Patsy & Merril, 2017). The responsibility for triggering the epidemic has been attributed to the drug OxyContin, a long-acting opioid analgesic launched into the market by the manufacturer Purdue Pharma in 1995 (deShazo *et al*., 2018; Kolodny *et al.*, 2015; Jones *et al*., 2018; Vadivelu *et al*., 2018, Bonnie, Ford, & Phillips, 2017).

Purdue Pharma is an American pharmaceutical company owned exclusively by the Sackler family. Arthur Sackler, the eldest of three brothers and a trained psychiatrist, obtained his wealth while innovating pharmaceutical marketing strategies in the 1960s, namely by extending doctors favours and gifts, funding experts to endorse a drug, and broadening the drug's treatment indications (Macy, 2018; Keefe, 2017; deShazo *et al*., 2018). Arthur's major pharmaceutical marketing success involved the anxiolytics, Librium (chlordiazepoxide) and Valium (diazepam), with reported record sales of more than a hundred million prescriptions in 1973 (Keefe, 2017).

In 1952, Arthur and his younger brothers, Mortimer and Raymond, bought a small pharmaceutical company called Purdue Frederick following the acquisition of a medical advertising agency and a medical news magazine (Macy, 2018; Keefe, 2017). Ten years later, Arthur was summoned by the Senate to testify regarding the integrated operation they owned, from drug production to drug marketing and sales, but the hearing amounted to no consequences (Keefe, 2017). The family business thrived and after

Arthur's death in 1987, the brothers bought his shares and changed the company's name to Purdue Pharma. OxyContin was soon to be released under the leadership of Raymond's son Richard, a trained physician as his father and uncles.

OxyContin contains the semi-synthetic opioid called oxycodone and a thin layer of coating that allows for controlled drug absorption. The launch of OxyContin came soon after the company lost its patent for MsContin, an opioid analgesic marketed in 1980 with the same type of coating allowing for the controlled release every 12 hours, but with morphine instead of oxycodone as the active ingredient.

Different from MsContin, the marketing campaign for OxyContin was crafted to rebuke the dangers of opioids' side effects, specially among physicians (Kolodny *et al.,* 2015; Jones *et al.,* 2018). The strategy was orchestrated based on results observed in focus groups studies, sponsored by the company, which revealed the biggest obstacle for prescription was the fear of the potential for abuse (Keefe, 2017). Efforts were drawn to inculcate into the medical community's practice that previous knowledge about opioid addiction was exaggerated and outdated, called by some "opiophobia" an understanding that led, according to some pain specialists, to the undertreatment of pain (Kolodny *et al.,* 2015; Vadivelu, *et al.* 2018; Jones *et al.,* 2018). The symptoms of withdrawal were either not discussed or attributed to the fabricated concept of "pseudo-addiction" an idea that claims withdrawal symptoms are due to unrelieved pain that requires larger doses of opioid instead of its tapering (Kolodny *et al.,* 2015).

According to pain specialists employed by Purdue Pharma, opioid use required destigmatisation. To that end, sales representatives were taught in three weeks training sessions how to reassure physicians the rate of addiction was low and argue its indications should be broadened (*ibid*). While MsContin was used primarily in palliative care and cancer pain, OxyContin was endorsed by the pharmaceutical companies, with the increasing support of medical associations, as safe for acute or chronic pain unrelated to cancer including arthritis, back pain, sports injuries, and fibromyalgia. The

plan was to extend the indications beyond cancer pain despite no good scientific evidence of effectiveness or safety (Jones *et al.,* 2018).

The marketing strategies were diverse, among them ads in medical journals, distribution of questionable scientific literature to medical offices, hiring of prominent physicians to endorse the drug, fraudulent scientific studies performed by the company, sponsoring of websites concerning chronic pain, distribution of objects with the brand's name, promotion of videos with patients' and physicians' testimonials, false claims of percentage of addiction, distribution of financial resources to continuing medical education and state medical boards, and distribution of OxyContin coupons for free prescriptions 30 days worth (deShazo *et al.,* 2018) .

The campaign financed by Purdue sponsored the APS, AAPM, FSMB, JC, and patient advocacy groups to legitimise and provide credibility to an opioid permissive new culture (Kolodny *et al.,* 2015). The development of guidelines endorsing opioids to treat chronic pain unrelated to cancer, solely based on expert consensus, was a collaboration between the AAPM, APS, and paid physicians by Purdue (deShazo *et al.,* 2018). According to Dr. Andrew Kolodny, the co-director of the Opioid Policy Research Collaborative, the result of the marketing strategy employed by Purdue Pharma resulted in a false idea that prescribing opioids for any pain was safe (Kolodny *et al.,* 2015). A permissive attitude was re-inaugurated, a rebirth from the pre-heroin era (*supra* 1.2).

In 2001, Purdue invested 200 million dollars with marketing expenses, the next year the number of prescriptions increased from 670,000 to 6.2 million prescriptions (Van Zee, 2009; deShazo *et al.,* 2018; Jones *et al.,* 2018). The notable increase in the number of prescriptions was the result of the employed marketing strategy, resulting in legal medical overprescription (Van Zee, 2009). Overprescription by physicians led to the creation of pill mills. A pill mill is a medical office or pharmacy that sells narcotics illegally for non-medical purposes. Through a prescriber profiling company owned by the Sackler family, Purdue Pharma's sales representatives knew which physicians were more prone to prescribe opioids, and therefore better sales targets (Patsy & Merril,

2017; Keefe, 2017). With that data in hand, Purdue was also aware of the existing pill mills and its locations, but opted not to alert authorities (Keefe, 2017).

Within five years, the company's revenue was 1 billion dollars a year and sales representatives shared 40 million dollars in bonuses in 2001 alone (*ibid*). When confronted with the increased rate of overdose deaths Purdue would respond by demeaning the addicted as "junkies" and condemning them for tainting their product capable of relieving people's pain (*ibid*).

Signs of abuse emerged within the first year of sales in small towns in central Appalachia (Macy, 2018). Reportedly, pills were being grounded and snorted in order to surpass the coating providing for the time release mechanism (*ibid*). In 2010, right about when the patent was about to expire, a new abuse-deterrent formulation for Oxycontin, one which prevented grounding and snorting of the pill, was approved.

As the epidemic grew stronger, the institutions previously permissive to the opioid surge began voicing concern. In 2003, DEA publicly denounced Purdue for deliberately minimising the risk of addiction. In that same year, the FDA signed a warning letter addressed to Purdue's executive vice president referring to two medical journal advertisements published in the *Journal of the American Medical Association* in 2002 affirming it omitted minimal safety information, minimised the risks associated to OxyContin, and recommended the drug to medical conditions with no substantiated clinical evidence. The letter concludes by requesting Purdue Pharma to immediately stop disseminating inaccurate information (Van Zee, 2009)

Purdue Pharma did not fully comply with the FDA's request and in 2007 lost its first federal lawsuit pleading guilty to criminal charges for misleading society with fraudulent misbranding (Meier, 2007). The company and three of its executives paid a total of $634 million in fines to federal and state agencies, and payments to settle civil litigations (*ibid*). In March 2019, Purdue Pharma settled another lawsuit based on charges against deceptive marketing, this time in Oklahoma, for $270 million. In

January 2019, the plaintiff Attorney General Maura Healey, of the state of Massachusetts, filed a lawsuit claiming ‘Purdue Pharma created the epidemic and profited from it through a web of illegal deceit’, furthermore, ‘Purdue misled them to use higher and more dangerous doses’, and , ‘Purdue deceived them to stay on its drugs for longer and more harmful periods of time’ (Healey, 2019: p.2). Along with Massachusetts, a total of 44 states, and more than 1,600 cities and counties have filed a similar lawsuit against Purdue. The company filed for bankruptcy in 2019.

Medical marketing tools were misused by Purdue Pharma and other pharmaceutical companies. Deceptive information with regard to the safety and effectiveness of the drug were endorsed by medical associations and pain medical experts with the financial support of Purdue Pharma. The permission of general direct-to consumer advertising, physician and associations gifts and donations, and free samples for patients and physicians opened the door to more abrasive and, at times, fraudulent activities.

Chapter 4. The FDA

The United States FDA is a federal agency responsible for preserving public health safety by regulating foods, drugs, vaccines, blood products, medical devices, radioactive equipment, cosmetics, veterinary products, and tobacco (FDA, 2018).

The FDA was conceived in 1930 from the Bureau of Chemistry within the Department of Agriculture created in 1906 to enforce the *Pure Food and Drugs Act*; a law which prohibited the commerce of misbranded and adulterated foods, drinks, and drugs. At the time, manufacturers were not obliged to submit any information to the Bureau prior to marketing their products. In 1912, the law was amended to prohibit fraudulent claims about drugs, but establishing intent was hard (*ibid*).

As a result of 107 deaths secondary to the ingestion of toxic ingredients found in the Elixir sulfanilamide, a new law was enacted in 1938: the *Federal Food, Drug, and Cosmetic Act* (FDCA) The FDCA, described on Chapter 9 of the United States Code (USC) under Title 21 named Food and Drugs, repealed the *Pure Food and Drugs Act* and expanded the FDA authority on matters of safety (FDCA Title 21 USC Ch.9 §321 to 399i). This act requires manufacturers to apply for approval and provide evidence that a drug is safe. Further progress in drug regulation came in 1962 when the FDCA was amended by the *Kefauver-Harris Act* that called for evidence of the drug's effectiveness in addition to safety information (FDA, 2018; FDCA Title 21 USC Ch.9 §355).

In this chapter, federal laws and regulations of the USC and the Code of Federal Regulation (CFR), with respect to advertisement, drug approval, labelling and pharmacovigilance will be discussed. The USC is the compilation of federal laws and the CFR is the official collection of rules determined by government agencies. The normative framework of these topics are enforced by primarily, but not exclusively, Title 21 of the USC, Title 21 of the CFR, and state legislation.

4.1 Advertisement, Drug Approval, Labelling and Pharmacovigilance

Medical advertisement in the United States allows direct-to-consumer and professional advertising of prescription drugs, disease awareness campaigns, and the advertisement of laboratory tests and health services (Schwartz & Woloshin, 2019). Between 1997 and 2016, spending on advertisements to medical professionals increased from $15.6 billion to $20.3 billion, but decreased in the percentage of overall marketing spending from 88% to 68% (*ibid*). This decline is due, in part, to the steeper increase in spending on direct-to-consumer advertising which rose from $2.1 billion in 1997 to $9.6 billion in 2016 (*ibid*).

4.1.1 Medical Advertisement

In the United States, direct-to-consumer advertising is permitted for both prescription and over-the-counter drugs (FDCA Title 21 USC §352; Title 21 CFR §202.1). Advertisement to the general public may be in the form of television commercials or published in print. It was approved into law in 1985 but was only widely used after 1997 when the FDA became more lenient towards the required obligatory list of side-effects reported by manufacturers (WHO, 2019).

Besides the United States, direct-to-consumer advertising is only allowed in New Zealand and has been criticised for increasing consumption of expensive drugs, encouraging off-label drug use, and misinforming the public (*ibid*). In 2015, the AMA called for a ban of direct-to-consumer ads with the purpose of curbing the demand of costly treatments that aren't necessarily clinically superior (AMA, 2019a). To this date, the ban has not been adopted.

In most cases, the industry is required to inform the FDA of advertisement content only after its distribution (FDCA Title 21 USC §352). Misleading information is illegal, and when detected by the FDA a warning letter is sent for correction prior to pursuing legal action (Title 21 CFR §202.1). Penalties and sanctions may apply.

Professional advertising, different from the direct-to-consumer ads, is dedicated to physicians and other healthcare workers.(Schwartz & Woloshin, 2019). As a rule, advertisement may not be false or misleading; for example, benefits and side effects must be equally informed (FDCA Title 21 USC §352; Title 21 CFR §202.1). Comparative statements are allowed when two or more randomised trials have demonstrated the drug's superiority (Title 21 CFR §202.1(e)). In 2016, less than half of the promotional material for new drugs or old drugs with new indications were reviewed by the FDA (Schwartz & Woloshin, 2019).

With regard to gifts and donations, federal statute forbids physicians to accept bribes in exchange for federal health care program reimbursements (Anti-Kickback Statute Title 42 USC §1320). However, this statute does not render gifts and donations illegal for there are exceptions that allow for this activity, such as, other types of remuneration and consulting services (Kracov & Davar, 2019). Sales representatives' visits are, essentially, not regulated by federal law. Non-binding ethics code by the AMA and the Pharmaceutical Research and Manufacturers of America stipulate limitations to both gifts and sales representatives visits to physicians (AMA, 2019b; PhRMA, 2019). State legislation and hospital policies may legislate to restrict these practices (Kracov & Davar, 2019). In 2010, the *Physician Payment Sunshine Act* was enacted to promote transparency of the gifts offered to healthcare providers (*infra* 4.2.4).

Continued medical education deemed independent from promotional activity is not regulated by the federal government (FDA, 1997). Sponsorship by manufacturers for educational activities is permitted and should follow the FDA non-binding guidance for the industry, issued in 1997, that stipulates what determines independent scientific and educational activities. The factors taken in consideration include: development of content and choice of speakers, disclosures regarding program funding and speaker's conflict of interests, relationship between activity organizer and the manufacturer, and audience selection (*ibid*). The FDA may be warned to investigate when these

considerations have been disregarded, however, the lack of regulation prevents legal proceedings (*ibid*).

Physicians are allowed to receive free samples of drugs by means of a written request (Title 21 CFR §203.30(a)). Manufacturers are responsible for keeping record of an inventory of distribution (Title 21 CFR §203.30(a); FDCA Title 21 USC §503). In 2010, with the enactment of the Affordable Care Act, manufacturers must inform the FDA of the inventory (Affordable Care Act §6004).

4.1.2 Drug Approval

In order to guarantee the public's health and determine the drug's safety and effectiveness, the FDA monitors the investigation of new or reformulated drugs, cosmetics, and medical devices (Bonnie, Ford, & Phillips, 2017). The approval of new drugs are submitted by the manufacturers through a New Drug Application form after successful completion of human studies (Title 21 CFR §315.50). Clinical studies are divided in phases: phase I trials are dedicated to determining the drug's pharmacokinetics and safety profile in a small pool of patients; phase II and III trials aim to verify safety in larger cohorts and to study effectiveness. While phase II trials are single-arm studies with a small cohort, phase III trials are randomised studies with a larger cohort defined by statistical measures to verify for the significance of the drug's effectiveness. These data are submitted to the FDA and analysed by a multidisciplinary team that includes professionals within the field of medicine, pharmacology, and toxicology (*ibid*).

Up to 1997, two phase III trials were needed to allow for the approval of a new drug, however, the *Food and Drug Administration Modernization Act* amended the FDCA and decreased the requirement to only one study in certain conditions (Bonnie, Ford, & Phillips, 2017). Currently, approximately one-third of approved novel therapeutics meet these conditions (Downing et al., 2014). A new indication attributed to a previously

approved drug requires a supplemental new drug application that can undergo a regular or abbreviated approval pathway (FDCA Title 21 USC §355 (j)).

In addition to the analysis of the studies' results, the FDA devises a qualitative benefit-risk assessment, occasionally with the help of an advisory committee composed of experts and stakeholders such as consumers and industry representatives, albeit the latter is not allowed to vote (Bonnie, Ford, & Phillips, 2017).

In 1995, OxyContin was approved by an abbreviated pathway indicated for reformulated drugs that relies on previously published scientific studies of safety and effectiveness (Bonnie, Ford, and Phillips, 2017; FDCA Title 21 USC §505(b)(2)). Dosages of 10, 20, and 40 mg were initially approved to be taken at an interval of 12/12 hours for the management of moderate to severe pain. Reportedly, the FDA's medical review officer observed no evidence of superior efficacy of OxyContin when compared to immediate-release oxycodone, the only advantage being increased dosage intervals (Van Zee, 2009). However, proving a drug is more effective than another is not necessary for the FDA to establish the drug has substantial evidence of efficacy for approval (Bonnie, Ford, & Phillips, 2017).

The following year, a bio-equivalency study report was submitted for the approval of higher dosages, 80 and 160 mg, indicated for patients tolerant to opioids. The dosages were approved despite the fact that by the company's own results, 68% of the oxycodone was immediately available when the tablet was crushed, an amount potentially fatal to the opioid-naive patient (Van Zee, 2009).

4.1.3 Labelling

Label is defined as the information contained in the box holding the product or the product itself (FDCA Title 21 USC §321(m)). As is the case with advertisement, labelling may not be misleading in accordance with the 1966 *Fair Packaging and Labeling Act*, further amended by the FDCA (*ibid* §321(n)). The FDA reviews the

manufacturer's label with the proposed drug's indications, instructions, and potential adverse effects, once the drug is approved for distribution (Bonnie, Ford, & Phillips, 2017).

In the case of OxyContin, the FDA approved the manufacturer's proposed label stating iatrogenic addiction was very rare when opioids are prescribed appropriately, and allowed for the statement that delayed absorption was believed to reduce the risk of abuse (Van Zee, 2009). The FDA examiner who oversaw the new drug approval was Dr. Curtis Wright, who within two years was employed by Purdue, a practice allowed by federal ethics rules which states a former senior official is allowed to join corporate boards after one year away from a public agency (Keefe, 2017; Kaplan, 2019).

The dosage interval of every 12 hours was the drug's main selling point and argument to guarantee insurance reimbursements when confronted by competitive opioids with lesser cost (Van Zee, 2009). Neither statements, that iatrogenic addiction is rare and that delayed absorption reduce the risk of addiction, were supported by evidence-based research (Bonnie, Ford, & Phillips, 2017).

Notwithstanding, when the FDA understands misleading or false information is disclosed by the label or drug advertising, it sends the manufacturer a warning letter, requiring revision and action upon the issues listed. Despite the expansion of medical marketing over the past decade, the number of violation letters for prescription drug advertisement decreased from 156 to 11 during the same period (Schwartz & Woloshin, 2019). Ultimately, the FDA may sue the company for false claims and retrieve payments for prescriptions paid by Medicare or Medicaid (Bonnie, Ford, & Phillips, 2017).

In 2001, in response to the FDA warning letter, OxyContin's label was corrected to clarify the incidence of addiction in patients with chronic pain was unknown, and the assumption of reduced risk of abuse was removed (*ibid*).

4.1.4 Pharmacovigilance

Pharmacovigilance is the activity of observing for adverse events undetected during the clinical trials once the drug is distributed to the general public. The magnitude of public's exposure to the drug amplifies exponentially once the drug is approved for sale. New adverse reactions not observed during clinical trials may surface to light, rendering it necessary for continued post marketing surveillance of adverse reactions. Adverse drug experience is considered as life-threatening, serious, or unexpected (Title 21 CFR §314.80(a)).

It is the manufacturer's responsibility to review all spontaneous notifications of adverse effects from any source, national or international (*ibid* §314.80(b)); this information must be submitted to the FDA at quarterly intervals for three years followed, and annually thereafter (*ibid* §314.80(b)(i)). Adverse event reports submitted by healthcare professionals, patients, and drug manufacturers are stored in the FDA's Adverse Event Reporting System database. Pharmacovigilance post-marketing studies are conducted by the manufacturers periodically, but not obligatorily (Bonnie, Ford, & Phillips, 2017).

According to Nachlis (2018), FDA regulations provide for strong influence prior to drug's approval and distribution, and weak oversight of post-marketing and pharmacovigilance activities. Between 2004 and 2016, 784,517 adverse events related to opioids were reported to the FDA's Adverse Event Reporting System database, among those, 158,181 (20%) were attributed to oxycodone (Veronin *et al*., 2019).

4.2 Outline of the Public Health Emergency Countermeasures

Public authorities have launched measures to halt the epidemic within different domains, such as, reduction of exposure to opioids, better treatment to those with opioid use disorder, research and development for non-opioid treatment and improved post-marketing surveillance (Califf, Woodcock, & Ostroff, 2016). This section will address,

not exhaustively, binding and non-binding measures dedicated to decrease opioid exposure and improve post-marketing surveillance implemented by public authorities. Albeit not specific to the opioid crisis, a provision of the Affordable Care Act to ensure transparency of gifts and donations for physicians and the FDA guidance for the industry with regard to continued medical education will be described.

4.2.1 The FDA Amendments Act and The SUPPORT Act

In 2007 the Food and Drug Administration Amendments Act introduced a new section to the FDCA with the Risk Evaluation and Mitigation Strategy Program (REMS) (FDCA Title 21 USC §505-1). REMS was created to add measures of safety control for specific drugs with risk of serious adverse effects. Under REMS, manufacturers may be required to provide a medication guide, or a patient package insert; in some instances, providers may have to undergo training to be allowed to prescribe the drug (*ibid*). In 2018, the FDA gained authority to order REMS for drugs with risk of abuse under T*he Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT) for Patients and Communities Act* (SUPPORT Act 2018).

The SUPPORT Act was passed by Congress to halt the opioid epidemic. The act amends the FDCA to strengthen FDA authority. As an example, the SUPPORT Act permits the FDA to warrant post-marketing studies by the manufacturers, not only for safety purposes but for drug efficacy, something previously required solely prior to drug approval (FDCA Title 21 USC §355). This specific amendment applies for opioids, a class of drugs commonly approved based on historical studies and for which data for efficacy of treatment for chronic pain remains inadequate (Staman, 2018).

Under the SUPPORT Act, a new section allowing the FDA Secretary to completely halt drug distribution in a scenario of high-risk probability of harm to the public was included to the FDCA (FDCA Title 21 USC §360). The Secretary may stop distribution for a determined period or request for a total recall (*ibid*).

4.2.2 Prescription Drug Monitoring Program

The prescription drug monitoring program is a state-level intervention that enables public officials to follow the amount of controlled substance prescribed and sold through an electronic database. It is used by physicians to verify patient's prior prescriptions for controlled substances (Kimberly *et al.*, 2018). Forty-nine of the fifty American states have passed legislation to implement prescription drug monitoring programs with the intent of reducing abuse, diversion and criminal activity (Davis, Johnston, & Pierce, 2015). The number of opioid prescriptions has since reduced nationwide, while increased use of illicit heroin and fentanyl has increased (*supra* 2.1).

4.2.3 CDC Guideline for Prescribing Opioids for Chronic Pain

In 2016, the CDC issued a guideline with recommendations on opioid treatment for chronic pain. The guideline was created to promote safety and avoid the incidence of opioid use disorder (Dowell, Haegerich & Chou, 2016). The authors reveal they reached twelve recommendations based on observational studies and low-quality randomized clinical trials; in addition, they note that no study of opioid therapy for longer than one year was available for the guideline development (*ibid*). The CDC, henceforth, recommends physicians should opt for non-opioid treatment for the management of chronic pain; opioids should only be used when benefits outweigh the risk (*ibid*). A management plan between physician and patient with regard to objectives and discontinuation when needed must be agreed upon by both parties. Different from what the initial label of OxyContin implied, that long-acting formulation protects from addiction, the CDC recommends starting treatment with immediate-release (*ibid*). In essence, although the guideline did not contra-indicate opioid therapy for chronic pain altogether, it implies opioids should be avoided, and, when unavoidable, cautionary steps must be undertaken.

4.2.4 The Physician Payments Sunshine Act

Professional marketing has been shown to alter physician's treatment choices (Datta & Dave, 2016). To manage financial relationships between the industry and healthcare professionals state policies have limited or banned gifts to physicians, while several academic institutions have prohibited pharmaceutical industry sponsored meals and speaker's fees (Medicare Payment Advisory Committee, 2017).

As part of the Affordable Care Act, the Physician Payments Act was introduced to ensure transparency of physician ownership or investment interests. The legislation obliges manufacturers to submit to the HHS, in electronic form, the name, value, date, and nature (honoraria, gift, food, travel, education and others), of any payments to physicians (Affordable Care Act §6002, 2010).

Chapter 5. Medical Opioid Use in Portugal

The DGS is the central public agency of the Portuguese Ministry of Health and possesses administrative autonomy (Regulatory Decree n.14/2012, of January, 25, art. 1). Powers and attributions of the DGS include: to monitor the determinants of health, to inform about the health status of the Portuguese population, to plan and implement the Health National Plans' programs and to define public health policies (*ibid*, art.2 al. b),c),d),f)).

In 2001 the DGS approved the National Plan for the Fight Against Pain. The plan was developed with the assistance of the medical association *Associação Portuguesa para o Estudo da Dor* (APED). Its implementation was preceded by research performed by a working group in 1999 that revealed 39.1% of the hospitals in Portugal offered services specific to pain treatment (*Direcção-Geral da Saúde,* 2001). The goal was to increase to 75% the number of dedicated pain services with different levels of complexity: level I, an established dedicated service with pain specialist; level II, a service with a multidisciplinary team apt to conduct research and teaching of health professionals; and level III, a multidisciplinary center for pain treatment affiliated to an academic institution (*Direcção-Geral da Saúde,* 2001).

In addition to the proposed structural changes, the plan offered general guidance with regard to pain evaluation and management. It mentioned opioid use for chronic pain unrelated to cancer remained controversial and should be reserved for specific situations, those which were not discriminated in the text, under the responsibility of experienced clinicians (*ibid*).

As part of the effort to raise awareness, the government created the national day for the fight against pain, celebrated for the first time on June 14th, 1999. As a result of these efforts, services dedicated to the management of chronic pain increased by 40% (*Direcção-Geral da Saúde,* 2008a).

The plan was followed by the Program for Pain Control in 2008 and the Strategic National Plan for Control and Prevention of Pain in 2013. Following these initiatives the management of pain was recognised as a medical specialty by the national physician's council; the *Ordem dos Médicos*. Strong opioids were included in the list of medications subsidised by the State and empirical knowledge regarding the prevalence of pain, both chronic and acute, in the Portuguese population, was sought (*Direcção-Geral da Saúde,* 2013).

From 2008 onwards, opioid treatment for chronic pain unrelated to cancer was recommended for those with moderate to strong pain refractory to other modalities of treatment. In addition, pain as the fifth vital sign was endorsed as a guiding principle of the program.

This chapter describes the structure and normative framework of medical opioid use in Portugal. Both binding and non-binding public instruments implementing policies aimed at increasing opioid availability will be discussed. The role of *Infarmed* and regulations with regard to drug approval, medical advertisement, labelling, and pharmacovigilance will be reviewed and compared to the American counterpart discussed in Chapter 4. Finally, data of increased opioids sales and use in Portugal is reported.

5.1 DGS: Guidelines and Regulations for Opioid Therapy

The DGS is responsible for defining norms and guidance for medical clinical practice (Regulatory Decree n.14/2012, of January, 25, art.2 al. a). The legal implications of clinical guidance vary within different countries, medical specialties, and the entity issuing the recommendations (Coppen, 2005). In some countries, guidelines can be used as evidence in a medical malpractice lawsuit, even when not mandatory (*ibid*). In Portugal, the DGS issues clinical recommendations classified as either informative or normative, following the former is voluntary, and the latter, mandatory.

The DGS stipulates four steps to draft and issue a new regulation. First, a working-group must elaborate a proposal; second, a public consultation is made available for 30 days; third, contributions gathered during consultation are revised; and fourth, the Scientific Commission of Good Clinical Practices validates the regulation according to the level of evidence and recommendation (*Direcção-Geral da Saúde,* 2019).

In June 2003, seven years after the launch of the fifth vital sign campaign by the APS, and one year after the JC revoked the concept by reinforcing "Pain *used* to be considered the fifth vital sign," the DGS issued a normative statement that implemented pain as a fifth vital sign (Baker, 2017: p.6; *Direcção-Geral da Saúde,* 2003) (*supra* 3.1). The rule, aimed at health regional administrations and healthcare services, was supported by the Commission of the National Plan for the Fight Against Pain and APED.

According to the recommendations described in the statement, pain should be systematically documented in a dedicated space on the vital signs sheet with the use of validated international scales of pain intensity (*Direcção-Geral da Saúde,* 2003). All alert patients with age equal to or greater than three years old should have their pain levels verified (*ibid*). The normative document, however, did not define guidelines for the clinical management of the identified pain. Opioid therapy was not mentioned in this document.

Despite its obligatory nature, the measurement and documentation of pain as the fifth vital sign had not been fully adopted by 2008 (*Direcção-Geral da Saúde,* 2008a). Clinical repercussions of its practice in Portugal have not been studied to date.

An informative, rather than normative, guideline, with respect to the use of strong opioids for chronic pain unrelated to cancer, was dispatched in 2008. The guiding principles were addressed to all physicians of the public health system and intended to:

> "… reduce the prevalence of moderate to strong chronic pain, increase adherence of the sick to therapy and improve their quality of life, reduce myths and prejudices associated to opioid medications and prevent its illicit use" (*Direcção-Geral da Saúde,* 2008b: p.1)[2].

The guideline clarifies the use of opioid for chronic pain unrelated to cancer has increased in parallel to results of clinical studies and systematic reviews of which the document makes reference to two studies: a systematic review and a meta-analysis. The systematic review concludes the short-term efficacy of opioids was good when compared to placebo but not to other modalities of pain treatment (Kalso *et al*., 2004). The same review states the short-term follow-up precludes any conclusion with regard to safety, specifically tolerance and addiction (*ibid*). The meta-analysis included 41 randomized trials with average duration of treatment of 5 weeks (Furlan *et al.*, 2006). All opioids were superior to placebo but only strong opioids were superior to other types of analgesia (*ibid*). Only 3 of the 41 trials contemplated following the patients for signs of addiction, therefore a significant conclusion with regard to long-term adverse effects was not possible. (*ibid*).

Despite the lack of evidence the guideline embraces the idea that concerns for tolerance and addiction are unfounded and notes that the World Health Organization pain scale indicated for patients with cancer is increasingly being applied to patients without cancer (*Direcção-Geral da Saúde*, *2008b*).

In a less permissive tone, the guiding principles invoke some restrictions: strong opioids should be considered a therapy of last resort, indicated to patients with moderate to severe chronic pain when refractory to other modalities of treatment (*ibid*). The patient must consent to treatment after fully informed of the risks and agree to comply to the rules, such as, take the medication as prescribed, not request medication from a different physician, and communicate immediately to the police if the medication is stolen (*ibid*).

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[2] This citation was originally in Portuguese and was translated to English by the author

Less than a year before the President of the United States declared the opioid crisis a public health emergency, another step was taken in Portugal to advance the treatment of chronic pain with opioids. An ordinance was passed in order to increase the subsidy for strong opioids. Up to this point the government co-payed for 37% of the drug's cost, under the new regulation opioids for moderate to strong pain, when prescribed in the setting of specialized pain or palliative services, receives 90% coverage of the costs by the State (Ordinance n. 329/2016*,* of December, 20, art.1 and n.1 of art. 3). The list of drugs contemplated in this ordinance includes the opioids previously made available by the state, buprenorphine, fentanyl, and morphine, in addition to new therapeutic options: hydromorphone, tapentadol, oxycodone and oxycodone with naloxone (*ibid, annex*).

Following the American footsteps, Portugal has embraced the fight against pain and the American narrative constructed in order to justify the liberal use of opioids. It is noteworthy that the Portuguese clinical guideline for opioid use in chronic pain is more cautious than the American recommendations supported in 1996 and bears more similarities to the CDC guideline published in 2016 (*supra* 4.2.3). Nonetheless, a normative structure that allows for easier access to opioids for the treatment of chronic pain has been placed despite the paucity of evidence for its safety.

5.2 The *Infarmed*

The government institution analog to the FDA in Portugal is the *Infarmed*: a public agency responsible for the management and control of drugs and medical devices with national jurisdiction *(*Decree-Law n.º 46/2012*,* of February, 24, n.1 of art.2*)*. *Infarmed* is a public institution under the supervision of the Portuguese Ministry of Health that disposes of financial and administrative autonomy (*ibid* n.1 e 2 of art.1) The institute is also an authority in several domains of activities related to health. It contributes to the development and implementation of health policies, supervises production, distribution, and advertisement of health products, monitors drug consumption, promotes research

activities, verifies that compliance to health codes, regulations, and laws are being respected, among others (*ibid* n.1 e 2 of art.3).

As is the case with the FDA, *Infarmed* is responsible for drug licensing, supervision of the advertisement's contents, labelling, and pharmacovigilance (Decree-Law n.º 176/2006, August, 30 n.2 of art.166). With the purpose of delineating the normative similarities and differences with its American counterpart a general, but not exhaustive, review of *Infarmed's* legal framework on these topics will be addressed in this chapter.

5.2.1 Medical Advertising and Labelling

When compared to American marketing regulations, Portuguese rules are notably more stringent. As is the case with opioids, drugs that require prescription, belong to the psychotropic class of medications, or participate in the National Health Service subsidy program are prohibited to be advertised to the general public. (*ibid* n.º 2 of art. 152º alíneas a), b), e c)). On the contrary, over-the-counter drugs may be advertised by television, internet, radio and others, however misleading information, and comparative advertisements to the public are unlawful and subject to sanctions (*ibid* n.º 1 of art. 153º).

Free sample distribution to patients is forbidden (*ibid* n.º 6 of art.153º*)*. In contrast with the United States free sample distribution to physicians is only allowed at the lowest dosage and with a box label displaying a free sample warning (Decreto-Lei n. 128/2013 of September, 5 al. c) and d) of art.162º) (5.1.1 *supra*).

Marketing of medications that require prescription is allowed to healthcare professionals (Decree-Law n.º 176/2006 of August, 30 art. 154º). Advertising campaigns to physicians do not require pre-approval by the *Infarmed*, however, the manufacturer is obliged to deliver a copy of the advertising material to the *Infarmed* within ten days of the publishing date (Decree-Law n.º 5/2017 of January, 6 art. 11º). The content of the advertisement may not be misleading; if a breach is identified *Infarmed* may open

inquiries to verify the possible offence (Decree-Law n.º 176/2006 of August, 30 n.º 3 of art. 150º and al. c) of art. 164º).

Sales representatives may visit physicians employed by the National Health Service so long they are registered with *Infarmed* (Despatch n.º 8213-B/2013 of June 24, n. 1º of art. 2º and n.1º of art 3º). Sales representatives' visits are limited to six per year for each institution and to a maximum of eight physicians per day (*ibid* n. 1º e 4º of art. 4º). This regulation contrasts with the unregulated American counterpart (*supra* 5.1.1)

Physicians may be subsidised to attend scientific meetings as long as the sponsorship does not influence medical practice and dispensing of the pharmaceutical product (Decree-Law n.º 176/2006 n.º 4 of art. 158º). Benefits in kind to physicians are not permitted, except when due to professional activity, such as, continued medical education, scientific communications, and drug marketing, as long as the payment does not oblige the physician to prescribe the drug (*ibid* n.º 1, 2 and 4 of art. 158º). The manufacturer is obliged to report the payment to *Infarmed* within 30 days (Decree-Law n.º 5/2017 of January, 6 art. n.º 10).

Private donations to the National Health Service must be approved by pharmaceutical companies and other companies related to health technology that may influence exemption and impartiality are not allowed (Decree-Law n.º 5/2017 of January, 6 n.º 1 of art. 9º). Pharmaceutical companies are not allowed to sponsor medical education events (*ibid* n.º 3 of art. 9º).

The manufacturer is criminally responsible for the complete and accurate information provided in the drug's label. (Decree-Law n.º 176/2006 of August, 30 art. 110º).

5.2.2 Drug Approval

The Medicine Act, enacted on August 30, 2006, is a decree-law dedicated to the regulation of production, quality control, safety, efficacy, commercial distribution and

pharmacovigilance of drugs in Portugal (*ibid* n.º 1 of art. 1º). The act unifies previous established norms and absorbs the European Union's legislations with regard to medication use, distribution and advertisement (*ibid* n.º 3 of art.2º alínea d), art. 54º).

There are different avenues through which *Infarmed* may grant drug approval for distribution. The procedure may be a centralised process performed by the European Medicine Agency, usual for new drug applications, or simplified (Botelho, 2019). The latter offers two possibilities: mutual recognition procedure when approved by another member state or as Portugal as the reference State and a decentralised procedure when the application is dispatched to different member states simultaneously (Decree-Law n. 176/2006 of August, 30 nº 1 e 2 of art.19º and al. a) of art. 40º).

As in the United States, clinical trials data are required for new drug approval, but if efficacy and safety have been observed within the European Union for at least 10 years, study results are exempted (*ibid* art. 20º*)*. The number of clinical trials required to approve a new drug is not specified (*ibid* nº 2 al. j) do art.15º). New therapeutic indications for previously approved drugs require the submission of new clinical trials to that end (*ibid* Art. 21º).

Once approved, medications that require medical prescription, as opposed to over-the-counter medications which do not require prescription, are only sold by pharmacies registered with *Infarmed* (*ibid* art. 79º). Over-the-counter medications are commonly used to treat mild medical conditions with a long established safety profile, while prescribed medications demand closer medical monitoring. Importantly, opioids do require a medical prescription, however, different from the United States any physician is allowed to prescribe opioids in Portugal, no special prescription pad or identification is needed (*supra* 4.1.2). Portugal issues both paper and electronic prescription. The electronic system, launched in 2012, maintains the complete prescription history of every patient, therefore, similar to the American Prescription Monitoring Program, physicians can check which medications were previously used.

Lastly, it is the *Infarmed's* responsibility to supervise and audit all pharmacies (Decree-Law n.º128/2013 of September, 5 n.º 1 of art. 176º) (*supra* 4.1.2), different from the United States that disposes of the DEA to survey irregular activities of controlled substances .

5.2.3 Pharmacovigilance

When the Portuguese National Pharmacovigilance System was implemented during the nineties only life-threatening adverse events were communicated by healthcare professionals and pharmaceutical industries (Decree-Law n.º 176/2006 of August 30 art. 169º*;* Herdeiro *et al.,* 2012). From 2007 onwards, pharmacies were normatively bound to join the surveillance collaboration (Decree-Law n.º 307/2007 August, 31 art. 7º). Concurrently, an internal pharmacovigilance system became an obligatory requirement for pharmaceutical industries applying for new drug approval (Decree-Law n.º128/2013 of September, 5 n.º 1 of art. 170º). As in the United States, the information gathered by the industry must be systematically shared with public agencies, both *Infarmed* and the European Commission*;* (Decree-Law n.º128/2013 of September, 5 n.º 1 al. b) and g) of art. 171º) (*supra* 5.1.4).

In 2010, European legislation broadened the definition of adverse events to include any unwanted reaction, such as therapeutic mismanagement, off-label use, and misuse; as a result, consumers gained access to the spontaneous notification system offered by *Infarmed* (Decree-Law n.º128/2013 of September, 5 n.º 1 of art. 171º). Portugal and the European Union are committed to communicate and share the results of their surveillance activities (Decree-Law n.º128/2013 of September, 5 n.º 1 of art. 174º).

Pharmacovigilance practices have evolved and broadened over the years. However, as is the case in the United States, it is the manufacturers' responsibility to carry post-marketing clinical studies upon request or voluntarily, the party less interested in detecting serious adverse events (Decree-Law n.º128/2013 of September, 5 n.º 1 of art. 175º**)** (*supra* 4.1.4).

5.3 Chronic Pain and Opioid Consumption in Portugal

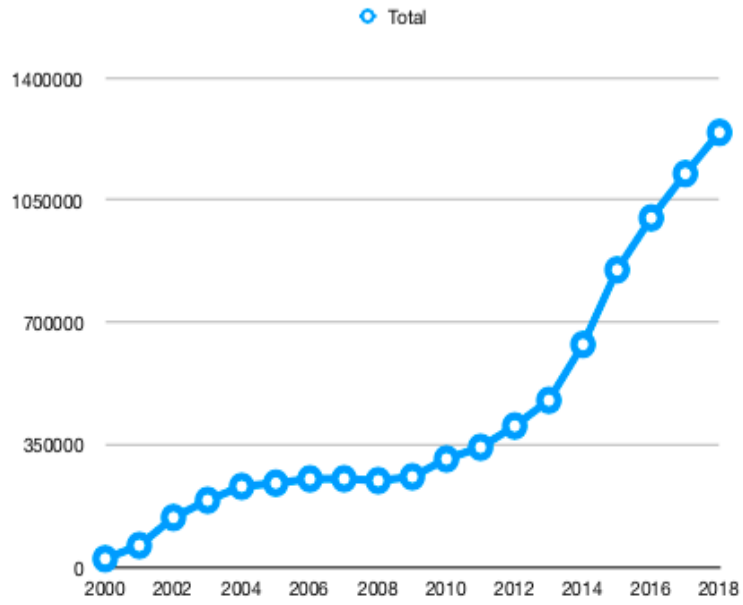
Portugal is home to an average population of 10 million people (PORDATA, 2019). A cross-sectional study performed between January 2007 and march 2008, estimated the prevalence of chronic pain with moderate to severe disability, defined by difficulties with home responsibilities, recreational activity, social activities and work, to be approximately 11% (Azevedo *et al*., 2013a). Based on the same cohort, Azevedo *et al.* (2016), estimated the economic impact of chronic pain costs Portugal 2.7% of the national gross domestic product and of this measure more than 50% are secondary to indirect costs: lost work days, early retirement, and unemployment. Approximately 4% of patients with chronic pain used opioids (Azevedo *et al*., 2013b).

According to data provided by *Infarmed* to the author, medical opioid consumption has increased approximately by 54-fold measured by the number of packages dispensed between 2000-2018; 22,922 packages dispensed in 2000 compared to 1,243,894 in 2018 (Figure 13). This measurement pertains to opioids dispensed in the outpatient setting including the following opioids: fentanyl, morphine, oxycodone, buprenorphine, hydromorphone, combination of oxycodone with naloxone and tapentadol. Oxycodone sales began in 2016 and increased by 130% between 2017 and 2018; from 3,577 to 9,650 packages (Figure 14). With the exception of morphine, the consumption of all types of opioids are trending upwards; most remarkably fentanyl, buprenorphine and tapentadol (Figure 14).

Tapentadol and buprenorphine have not been previously addressed in the dissertation. Buprenorphine is a partial opioid agonist, used for pain treatment as well as for opioid use disorder management, its consumption increased from 3,780 packages in 2000 to 352,011 in 2018 (Figure 14). Tapentadol was approved by the European Medicine Agency in 2010. As tramadol, it has dual action; it inhibits norepinephrine uptake and acts on opioid-mu receptors (Mosele, Almeida, & Hess, 2018). Reportedly, it has less

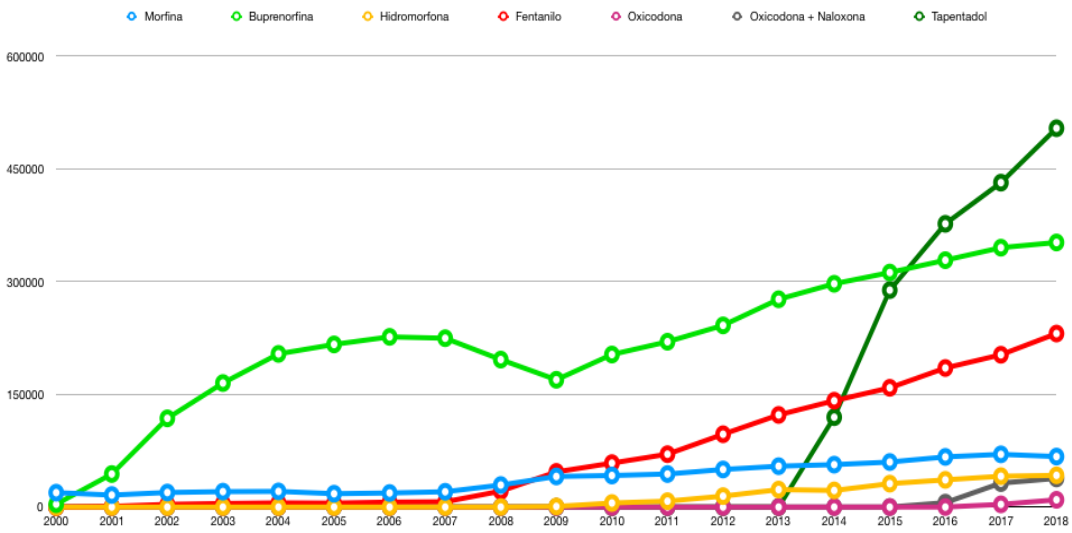
gastrointestinal side effects and develops less tolerance (Mosele, Almeida, & Hess, 2018). In six years, its use has increased from 21 packages in 2012 to 936,238 in 2018 (Figure 14).

Figure 13: Total opioid consumption: Health National Service/Portugal, 2008-2018.



Source*: CCMSNS (Centro de Controlo e Monitorização do SNS)* Center of Control and Monitoring of the National Health System
In the period between January 1, 2000 and December 31, 2013, the data refer to medicines reimbursed and dispensed on an outpatient basis to users of the National Health Service in Mainland Portugal. In the period between January 1, 2014 and December 31, 2018, the data refer to medicines reimbursed and dispensed on an outpatient basis to users of the National Health Service and public subsystems, in Mainland Portugal. This database does not include medicines related to the hospital environment (translated to English by the author).
Methadone consumption is not included.
Graph produced by the author with data provided by *Infarmed* (*supra* Methods).
Methadone consumption is not included

Figure 14: Opioid consumption, by type: Portugal, 2000-2018.



Source*: CCMSNS (Centro de Controlo e Monitorização do SNS)* Center of Control and Monitoring of the National Health System

In the period between January 1, 2000 and December 31, 2013, the data refer to medicines reimbursed and dispensed on an outpatient basis to users of the National Health Service in Mainland Portugal. In the period between January 1, 2014 and December 31, 2018, the data refer to medicines reimbursed and dispensed on an outpatient basis to users of the National Health Service and public subsystems, in Mainland Portugal. This database does not include medicines related to the hospital environment (translated to English by the author).

Methadone consumption is not included.

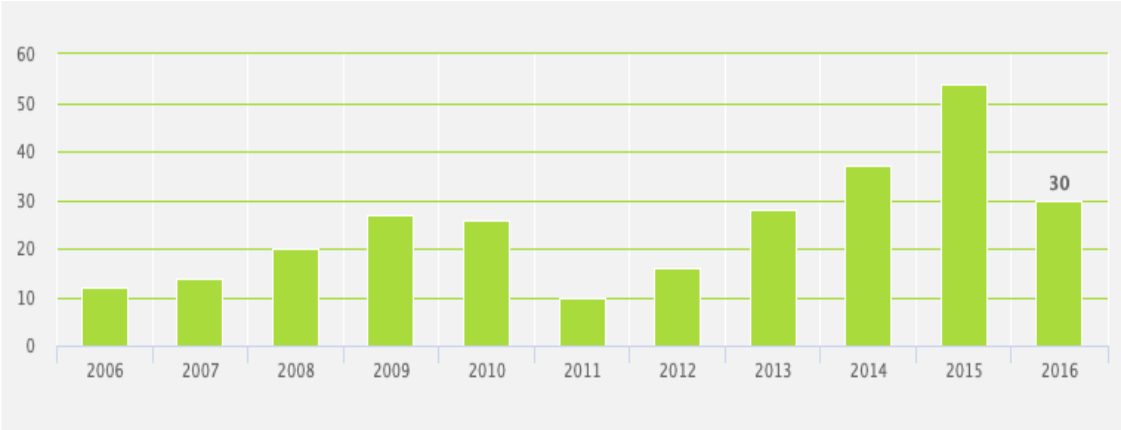
Graph produced by the author with data provided by *Infarmed* (*supra* Methods).

This data does not discriminate between different pain etiologies. Therefore, it is not possible to conclude whether pain management for cancer patients, pain management for acute and chronic pain unrelated to cancer, or all of them have expanded.

According to the EMCDDA (2019), drug-induced mortality rate among adults aged 15-64 years increased between 2011-2015 in Portugal and is currently in decline at approximately 4 deaths per million; three in every four were attributed to opioids although combinations with other drugs were frequent (Figure 15). Five in every one thousand individuals were deemed high-risk for opioid use in 2015; the European average ranges between 0,5 and 8 (EMCDDA, 2019). The total number of patients requiring opioid substitution treatment declined from 24,312 in 2007 to 16,888 in 2017 (EMCDDA, 2019). Opioids are responsible for 40% of admissions to specialised drug treatment, a reduction compared to over 60% in 2008 (EMCDDA, 2019). Heroin users seeking treatment decreased from 3000 to approximately 1000 between 2009-2012 and has maintained this level since (EMCDDA, 2019).

Importantly, an increase in opioid use disorder and drug-induced mortality have not been observed in parallel to the increase in medical opioid use, however, 2018 and 2019 indicators are not yet available.

Figure 15: Overdose deaths: Portugal, 2006-2016. (EMCDDA, 2019)



PART II

Chapter 6. Opioid Use in Portugal: Perceptions of Portuguese Key-Informants

The author was particularly interested in exploring key informant's views and perceptions of medical opioid use in Portugal considering the adequacy of the normative structure in effect in light of the opioid prescription epidemic observed in the United States.

6.1 Methods

6.1.1 Design

The author conducted a qualitative study with semi-structured interviews. Health professionals involved with pain management and members of medical societies or active in national public health governance were considered potential key-informants. Key-informants were recruited via email to public agencies, medical associations, and non-governmental organisations, namely: Intervention Unit in Addictive Behaviors and Dependencies/*Serviço de Intervenção nos Comportamentos Aditivos e na Dependências*, *Infarmed*, DGS, Portuguese Association for the Study of Pain/ *Associação Portuguesa para o Estudo da Dor*, Portuguese Institute of Oncology/ *Instituto Português de Oncologia*, Order of Portuguese Physicians/*Ordem dos Médicos de Portugal ,* Portuguese Society of Anesthesiology/*Sociedade Portuguesa de Anestesiologia,* Order of Portuguese Nurses/*Ordem dos Enfermeiros em Portugal,* Portuguese Association for Addiction/*Associação Portuguesa de Adictologia,* and Narcotics Anonymous/*Narcóticos Anónimos*. The invitation explained the nature of the study and asked for indications of pertinent key-informants with respect to opioid use in Portugal. Following the snowball sampling technique, interviewed key-informants were asked for further recommendations of other representatives with expertise within the subject.

6.1.2 Data Collection

A semi-structured guideline composed of eight questions was developed by the author (Appendix A). The interviewees were asked about their perceptions concerning the opioid use in Portugal, adequacy of the Portuguese regulatory framework and use of this class of medication to treat chronic pain unrelated to cancer. Participants read and signed the informed consent form prior to the interview (Appendix B). Interviews were anonymised and kept confidential. Interviews were conducted in Portuguese, face-to-face, and in both the cities of Lisbon and Porto. Data collection depended on institutional response, as well as on suggestions from interviewed key-informants, therefore, theoretical saturation of the data was not sought. Interviews were conducted during the months of October and November 2019.

6.1.3 Data Analysis

Interviews were recorded and transcribed verbatim by the author. Data analysis of the transcripts was performed using thematic analysis, a method of qualitative descriptive research. Thematic analysis is considered a basic tool of qualitative analysis adaptable to different theoretical frameworks, therefore unbound to a specific theory (Braun & Clarke, 2006). The process is flexible and iterative being constantly revised upon new observations (*ibid*). Its main purpose is to detect common themes among the gathered data pertaining to respondents views, underlying ideas, assumptions and description of phenomena (*ibid*).

Manually, the author reviewed the data and created codes to form themes that represented the main ideas and topics discussed by the key-informants. The identification of themes followed the process proposed by Vaismoradi, *et al.,* (2016) which divides the process in four phases: initialization, construction, rectification and finalization. These phases consist of reading and rereading transcripts while taking notes, labelling and comparing, connecting themes to previous knowledge and developing a narrative (Vaismoradi, *et al.* 2016).

Themes were analysed at a semantic level rather than interpretative level: the goal was to address, concretely, key-informants views on the subject as opposed to reveal the origins of the underlying perceptions. Participants' direct citations were translated to English by the author

Results may be interpreted through both deductive and inductive reasoning. While, a deductive process introduces an idea and explores the data with the intent of responding to a predefined hypothesis, inductive bears no obligation to answer any previous question or fit into a specific framework; with inductive analysis the researcher is longing for new perspectives (Braun & Clarke, 2006).

This dissertation begins with the assumption that health law may have played a role in the emergence of the opioid epidemic and that an overview of the Portuguese normative structure of medical opioid use may reveal strengths and weaknesses in face of this threat. The author, for this reason, used a mixed approach for data analysis, at times deducing upon observations documented in the description of Part I, and other times expecting new perspectives to emerge from the key-informants.

6.2 Results

In total, the author interviewed five key-informants: four physicians and one nurse. Snowballing sampling resulted in two of the five interviews. Interview duration ranged between twenty and forty minutes. Five themes were identified: limited efficacy of opioid therapy, underutilisation of opioids in Portugal, preventive measures for opioid overuse, physician relationship with the pharmaceutical industry and specific traits of the United States. Each theme is described below in detail.

6.2.1 Limited efficacy of opioid therapy

The limitations of opioid therapy to treat chronic pain was consensual among respondents. The views shared described an important role for opioids in pain management but not in every circumstance or every patient. Participants disclosed the following observations:

> *There is a group of patients that benefit* {from opioids}*, however, not all of them, and this seems to me the point in case and the future of the role of opioids to treat chronic pain, knowing how to identify patients…*

> *…* {opioids} *however should not be viewed as a panacea, meaning it is useful for every patient and any type of pain, because that is not true.*

> *Opioids should not be viewed as first-line treatment for chronic pain unrelated to cancer, however when other strategies fail, opioids frequently or in many occasions have an important role.*

> *However, we should not exaggerate and say that opioids are not useful, that opioids are poisonous, and it is something that we should avoid. I think somewhere in the middle is the balance, either always or never.*

Despite the acceptance that even if limited there is some role for opioids for the treatment of chronic pain there is concern for the lack of robust data to defend this practice.

> *There was a transposition of the principles we use for treatment of oncological to non-oncological chronic pain, almost immediately, without large studies to defend that with large robust results.*

An understanding that pain management has several different tools and should be addressed by a multidisciplinary team places opioids as part of a broader armamentarium for pain control.

> *There must be a multimodal approach and our unit has pharmacologic treatment, of course, with opioids, acupuncture, some invasive techniques with* {nerve} *blocks and infiltrations, we value very much functional rehabilitation, and that is why we have a physiatrist.*

Opioid's limitations and its potential side effects should influence patient education regarding efficacy and side effects. The following citations reflect these concerns:

> *There was an increase in the use of opioids for the treatment of pain and chronic pain, but it is necessary to effectively ponder its efficacy to people.*

> *I think it is the education, education takes time, explaining a disease takes time, but this is what we will face, and in fact, be very honest with ourselves, with the staff and with the patients, tell them what we are doing and the importance of what we are doing.*

> *Because we are authorising a medication not exempt of risks, and that after some time does not benefit patients, it does not make sense to keep it indiscriminately only due to the assumption that if stopped the situation will worsen*.

6.2.2 Underutilization of opioids in Portugal

In the past, opioid therapy was restricted to treat severe pain in patients with cancer, it was the participants' opinion that opioids were essentially under prescribed. As one participant said:

Ten years ago, I could count on my fingers how many patients would show up taking strong opioids, many show up now.

Different reasons for the scarce use of opioids were proposed by the participants, among them the heroin epidemic that afflicted Portugal in the nineties and the lack of medical education in pain management. These perceptions are indicated in the following lines:

In Portugal we were always very careful with drugs containing opioids, there was a serious heroin epidemic that prompted opioid demand including cough syrup with codeine, gradually these medications were removed from the market, therefore, the physicians never prescribed them a lot except in the situation of cancer.

In Portugal, fortunately, to a certain point, people are afraid of opioids, the physician himself, and therefore, {they} *don't use it, rather they prefer to ignore it than to test it, that has been the rule in Portugal.*

According to one participant, the opioid underutilisation justifies the recent increase in opioid prescriptions:

More opioids are prescribed now than 10 or 15 years ago, this is not, however, necessarily alarming, because we may be facing a difference between not treating pain entirely or treating something, I think this distinction is important, from zero to ten it is not necessarily an abuse, is it?

For others, public campaigns for medical awareness and pharmaceutical medical marketing were considered important factors for the increase in opioid dispensing by physicians of various medical specialties. Views regarding changes in medical practice are demonstrated in the following extracts:

A lot of medical education and divulgation around the theme of pain occurred in the past 15 year, and I think that has contributed decisively to this shift, also, coming from the pharmaceutical industry, there has been a more active marketing.

We have greater awareness of the professionals for the treatment of pain, for the identification of pain but also I think there is a stronger influence of the marketing from the pharmaceutical industry.

A*n increase in opioid prescription, in urgency units, as well as from physicians of other specialties, orthopedic, general medicine, family medicine, increased exponentially.*

6.2.3 Preventive measures for opioid overuse

Participants alerted that aberrant opioid prescriptions are beginning to surface and that preventive measures to avoid inadequate opioid use are needed. Concerns for physician mismanagement of the use of opioids were cited as following:

In our units, patients arrive with opioid prescriptions, sometimes in high doses, with no indication for opioids, much less for those dosages.

When clinicians do not know them {opioids} *well, when they do not master their indications, their contraindications, their complications, this opens the door to bad practice.*

At times, an opioid is not the most indicated, not for the patient profile, or the clinical context, and following that, the patient did not have supervision or clinical follow-up.

Different preventative measures were recommended by the participants. Among them, improved medical education in pain management, systematic monitoring of opioid use and distribution and careful patient evaluation and follow-up are described below.

It is important that all professionals are educated to treat pain, but also to refer patients in refractory situations.

A broad training is needed, namely at the level of younger doctors who have not gone through those phases {of the Portuguese heroin epidemic}.

I would like to see monitoring, who is prescribing? What type of patients? Which types of strong opioids? I would like to know that.

Hardly a patient {with chronic pain} *will take 20 minutes in his first visit, the average time will be one hour or more in this first encounter.*

The patient profile is very important, previous psychological ailments are taken into consideration, it is always valuable to verify if the patient has the profile in terms of adherence to safety and the context the patient lives in.

Consensually, participants agreed the public program of electronic prescription is an important tool to aid with monitoring of opioid consumption for the prevention of opioid misuse.

It is an effective safety measure that allows us to precociously identify situations of bad use or abuse of opioids.

Through electronic prescription, Infarmed may track the medication from the moment it is prescribed by the physician to the moment it is filled to the patient.

6.2.4 Physician relationship with the pharmaceutical industry

Participants shared a positive perception of the pharmaceutical industry as a provider of access to continued medical education. Their appreciation can be verified in the following excerpts:

I believe the pharmaceutical industry has a very important role in medical education, because it is with the help of the pharmaceutical industry that we obtain some quality education, look, I am here at this conference for which my department will not pay the registration, if it wasn't for the pharmaceutical industry I would not be able to attend.

Nowadays, more and more, depending on the socioeconomic conditions of health professionals in question, if there is no support from the pharmaceutical industries, health professionals in Portugal are isolated from the world.

The opinion that the pharmaceutical industry is a positive asset was corroborated by the wide acceptance of the legislation concerning the relationship between physicians and the pharmaceutical industry. Most participants deemed protective the need for full disclosure regarding industry gifts or donations and possible conflicts of interest for a

healthy relationship between physician and industry. Commendation for the Portuguese legislation regarding by participants are shown by these quotes:

> *These situations are very well regulated by the Infarmed, in terms of support I have to prove to my department that I will attend the conference and I have to declare who is sponsoring it, if myself or a laboratory, and how much is being spent.*

> *Legislation controls without limiting access, I honestly don't see the necessity of changing the existing legislation in Portugal in its substance, what we have now is adequate.*

> *Everything is transparent, I have to sign contracts and declare my conflicts of interest, everything is notified on Infarmed.*

6.2.5 Specific traits of the United States

The risk of having a similar opioid epidemic in Portugal was not entirely rejected by the participants, however, they argued differences between countries with respect to medical malpractice lawsuits and marketing legislation were highlighted as protective and suggestive that such an occurrence is unlikely.

Participants remarked access to treatment for pain is a human right. Still, while due diligence to the respect of this right may be taken to the court of law in the United States this practice is not common in Portugal. This perception is observed in the following passage:

> *They* {Americans} *are very aggressive in the way they sue physicians, namely, if you don't treat my pain well, I will sue you, this does not happen in Europe.*

In agreement with this dissertation's premise, which emphasis the role of health law in public health, the absence of direct-to-consumer marketing was considered an important difference between American and European legislation, as observed in the following excerpt:

> *There are many different things in the United States when compared to Europe, pharmaceutical industries may market medications directly to patients, in Portugal and Europe this does not happen, and I think that is very good, I believe this should not occur, this is not the same thing as selling potatoes in schools, right?*

6.3 Discussion

The author's findings was that although key-informants acknowledge the limitations of opioid use for the treatment of chronic pain unrelated to cancer they share the opinion that there is clinical indication for a subset of patients, despite scant empirical evidence to support it.

Several studies carried out to address the effectiveness of opioids in patients suffering from chronic pain, lasted for only 5 weeks to 3 months and did not attest for the sustained response to treatment in the long term. (Furlan *et al*., 2006; Martell *et al*., 2007, Chou *et al*., 2009; Papaleontiou *et al*., 2010; Chou *et al*., 2015; Busse *et al*., 2018). In 2018, Busse *et al*. reviewed 96 randomised control trials involving 26,169 patients, of those, 42 studies followed patients for longer than 3 months. When opioids were compared to placebo a slight superiority was reported for opioid treatment, however, the level did not reach the threshold for minimally important difference, a

measurement created to quantify the least amount of improvement deemed meaningful by the patient (Busse *et al*., 2018). The lack of pain relief in the long-term was confirmed by Veiga *et al.,* (2019) in a two-year multicenter prospective cohort study completed in Portugal. Furthermore, safety data on opioid use disorder in the long-term is scarce, due to the short duration of the trials and variations within definitions and methods to identify opioid use disorder (Chou *et al*., 2015).

Participants' impressions on the increase of opioid use are consistent with the data depicted in this dissertation (*supra* 5.3). Opioid underuse was attributed to Portugal's past difficulties with heroin addiction, but also to physician's fear of using opioids. At this point, one could argue fear was due cautiousness and that the jargon 'opiophobia' was the result of marketing strategies employed in the United States and disseminated by medical guidelines based on expert consensus alone (*supra* 3.1). Similarly, the possible transition to opioids overuse was deemed, by participants, to be secondary to public awareness campaigns and increased advertisement. The role of American marketing and medical knowledge production is verified by the adherence to the concepts of pain as a fifth vital sign and the opioid use for chronic pain unrelated to cancer both of which have been embraced by Portuguese and other European countries' medical practice and legislation (Levy, Sturgess & Mills, 2018).

As noted by respondents, signs of excessive and unwarranted opioid prescriptions are beginning to show. To counteract opioids overuse, participants suggested specialised pain management education and closer monitoring of opioids prescription, dispensing and sales, and careful patient evaluation. The national electronic prescription program was identified as a preventive measure to opioid mismanagement. With this system, like the American prescription drug monitoring programs, prescriptions signed electronically are accessible to any physician, and, therefore, overprescribing is avoided (*supra* 4.2.2). In the United States, prescription drug monitoring programs have shown to reduce opioid prescribing rates and overlapping prescription indicating the program prevents, to some extent, opioid misuse (Strickler *et al*., 2020; Strickler *et al*., 2019).

Physician advertising and ties with the industry were, in the contrary, not deemed inappropriate by participants, in fact, most considered essential the pharmaceutical sponsorship for continued medical education. Participants argued that industrial ties are acceptable once notification of gifts and donations are obligatory through the *Infarmed's* electronic system, as in the United States with the Physician Payments Sunshine Act enacted in 2010 (*supra* 4.2.4). In the United States, empirical evidence has shown association between gifts and brand prescriptions and reduced industry transfers to physicians once obligatory public reporting was implemented (Brunt, 2019).

Two participants viewed excessive medical litigation in America as a possible culprit to the opioid epidemic. Taking into consideration that access to pain treatment is a human right, their idea was that the legal duty to relieve pain may have pushed physicians to be overzealous. Families who have sued physicians in the United States for negligence of pain treatment have managed to recover meaningful damages by jury's verdicts (Rich, 2001). Historically, it has been the fear of legal sanction when prescribing opioids that has guided medical practice (Dineen & DuBois, 2016) (*supra* 3.1.2). It is not clear if fear of litigation for undertreating pain had a significant role in the epidemic.

6.4 Study Limitations

The research question of this study is original and although the author interviewed few participants the aim of this study was not to achieve theoretical saturation but rather to interview pertinent healthcare professionals specialised in the field of pain management in Portugal. Participants were reached through direct contact of public institutions and medical associations as well as by personal suggestions of participants themselves, therefore, promoting a robust ecological validity. Nonetheless, the study's external validity would have been stronger if greater participation from the contacted institutions was achieved (Nowell, 2017).

Despite good data collection, face-to face, which strengthens credibility, results were not shared with participants after the interview and the data were interpreted solely by the author, hence, internal validity is weak (Nowell, 2017). A robust amount of transcribed data was cited in order to circumvent this limitation.

Chapter 7. Dissertation´s Final Conclusions

It is undeniable that the American opioid crisis was triggered by the pharmaceutical industry and perpetuated by opportunistic individuals, including physicians and private companies willing to commit fraud (*supra* 3.2). However, it is also patent that permissive health laws allowed for these practices to be set in motion. Legislative counter-measures such as the SUPPORT Act and the Physical Payments Sunshine Act, which, among others, added measures of safety to opioid patient package insert and strengthened the control of gift and donation from the pharmaceutical industry to physicians, respectively, are evidence that health laws improvements were required to prevent further injudicious actions (*supra* 4.2.1 and 4.2.4).

The SUPPORT act empowered the FDA to demand post-marketing studies, henceforth, rendering the process of drug approval more safe, especially with drugs approved based on historical studies, such as opioids. The act also allows for a complete stop of drug distribution when deemed appropriate by the FDA secretary, enabling a prompt response rather than a delayed one and granting relevance to data gathered by pharmacovigilance activities.

Drug approval and pharmacovigilance procedures are very similar among the two countries, however, different from the United States, Portugal does not allow direct-to-consumer medical advertisement of drugs that require prescription, and advertising to physicians is strictly controlled; the number of sale representative's visits to physicians is limited and, gift and donations are kept to a minimum (*supra* 5.2). Furthermore, legislative counter-measures implemented in the United States to halt the epidemic, namely, strict transparency of industry ties to physicians and prescription control through an electronic system, are already part of the Portuguese health laws framework.

Besides intensive marketing strategies, pharmaceutical companies, most evidently Purdue Pharma, succeeded in modifying non-binding rules present in medical guidelines. Pain management guidelines were systematically altered in the United States

with the approval of medical associations and pain management experts to impart the idea that opioid was safe for chronic pain unrelated to cancer. This premise was distributed world wide promoting guideline changes and creating an unsafe perception of the risks of opioid treatment.

It is noteworthy that changes in behaviour of medical practice with regard to broadened indications for opioid use, despite limited data to support it, have crossed the Atlantic and along the years seeped into Portugal's national guidelines. In specific, normative changes such as the adoption of pain as the fifth vital sign and opioid use for chronic pain unrelated to cancer were approved (*supra* 5.1). This is particularly concerning when opioids can be freely prescribed by any physician, with no specific prescription or training required, in the setting or rising opioid sales (*supra* 5.3).

Portuguese pain specialists who participated in this study argue that national legislation ruling opioids' prescriptions, sales and marketing is adequate to maintain appropriate access to pain treatment while avoiding medical overprescription (*supra* 6.2.4). Nonetheless, they suggest that measures to prevent opioid mismanagement are required, among them, specialized education in pain management for healthcare professionals, patient education about opioids risks and benefits, and systematic surveillance of opioids' sales (*supra* 6.2.3).

In conclusion, there is indication that lenient laws with relation to drug approval, sales, marketing, and labelling have partly contributed to the American epidemic. While relevant health laws enacted in the United States to halt the epidemic are in force in Portugal, implementation of preventive measures for opioid mismanagement by physicians are recommended.

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Appendix A: Semi-Structured Interview Guiding Questions

1. Have you observed changes in the use of opioid drugs in the last decade in Portugal
2. What is your opinion on the use of opioids for the treatment of chronic pain not related to cancer?
3. What are the positive and negative aspects of the normative order that govern the control of the class of opioid drugs in Portugal?
4. What is your impression of the concept of pain as the "fifth vital sign"?
5. What is your opinion on the laws that regulate the role of the pharmaceutical industry on medical practice in Portugal?
6. Would you recommend changes to the Portuguese regulatory framework on these topics?
7. In your opinion, is it possible for the American epidemic to reproduce in Portugal? Why?

1. *Observou mudanças no uso de medicamentos opióides nesta última década em Portugal*
2. *Qual é a sua opinião sobre o uso de opióides para o tratamento da dor crônica não relacionada ao cancro?*
3. *Quais são os aspetos positivos e negativos da ordem normativa que regem o controlo da classe de medicamentos opióides em Portugal?*
4. *Qual a sua impressão sobre o conceito de dor como o "quinto sinal vital"?*
5. *Qual a sua opinião sobre as leis que regulam o papel da indústria farmacêutica sobre a prática médica em Portugal?*
6. *Recomendaria mudanças para o quadro normativo português nestes temas?*
7. *Na sua opinião, é possível que a epidemia americana se reproduza em Portugal? Porquê?*

Appendix B: Informed Consent

Researcher: Anna Maria Delios

Advisor: Prof. Paula Lobato de Faria, PhD

Organization Name: National School of Public Health / Universidade Nova de Lisboa (ENSP / UNL)

Project Name: The American Opioid Epidemic from a Normative Perspective: Lessons for Portugal

Study information

Within the scope of the master's degree in Public Health at ENSP / UNL and under the guidance of Dr. Paula Lobato de Faria, PhD, professor at ENSP / UNL, I invite you to participate in a study on the use of opioid drugs and the regulations for their use in the treatment of non-cancer-related pain in Portugal, given the epidemic that is taking place in the United States United.

The purpose of the interview is to investigate the perceptions and experiences of key informants about the use of opioids in Portugal and the regulatory control that governs the use of this class of drugs.

Your participation in this study is entirely voluntary, with the right to refuse the interview or cancel your participation at any time during the interview. The interview will last 30-40 minutes. In order to accurately record your answers and assist in the

subsequent analysis of data, we intend to record the interview and for that we request your consent. Personal data, such as your name, the position you hold, the position you hold, and the institution you belong to will remain anonymous. After 4 months from the date of the interview, the recording will be deleted. The collected data will be analyzed and published only for academic purposes, in the form of a master's thesis, presentations at congresses and publication in scientific journals.

If you have any questions feel free to ask. After the interview we will remain available for any questions that may arise.

Consent

I was invited to participate in the study on "The American Opioid Crisis in Public Health from a Normative Perspective: Lessons for Portugal". I read the information above and had the opportunity to clarify my doubts. I voluntarily accept to participate in this study and consent to the recording in my interview.

Name of Participant:

Signature:

Date:

I explained the information in this document in detail to the participant and made sure that he / she understood that a recorded interview will be conducted. I confirm that the participant has had the opportunity to ask questions about the study, and that all questions have been answered. I confirm that consent was given voluntarily.

A copy of the consent was made available to the participant.

Researcher's name and signature:

Date:

Investigadora: *Anna Maria Delios*
Orientadora: *Prof. Doutora Paula Lobato de Faria*
Nome da Organização: Escola Nacional Saúde Pública/ Universidade Nova de Lisboa (ENSP/UNL)

Nome do Projeto: *A Epidemia Americana do Opióide sob uma Perspetiva Normativa: Lições para Portugal*

Informação sobre o estudo
No âmbito do mestrado em Saúde Pública da ENSP/UNL e sob a orientação da Prof. Doutora Paula Lobato de Faria, docente da ENSP/UNL, convido-o a participar num estudo sobre o uso de medicamentos opióides e os regulamentos para o seu uso no tratamento da dor não relacionada com cancro em Portugal, face à epidemia que decorre nos Estados Unidos.

O objetivo da entrevista é investigar as perceções e experiências de informadores-chaves sobre o uso de opióides em Portugal e o controle normativo que rege a utilização desta classe de medicamentos.

A sua participação neste estudo é inteiramente voluntária, tendo o direito de recusar a entrevista ou cancelar a sua participação em qualquer momento da mesma. A entrevista terá uma duração de 30-40 minutos. A fim de registar fidedignamente as suas respostas e auxiliar na análise posterior de dados, pretendemos gravar a entrevista e para tal solicitamos o seu consentimento. Dados pessoais, como o seu nome, o cargo que ocupa, a função que exerce, e a instituição a que pertence permanecerão anônimos. Após 4 meses da data da entrevista a gravação será apagada. Os dados recolhidos serão analisados e publicados apenas para fins académicos, em formato de tese de mestrado, apresentações em congressos e publicação em revistas científicas.

Caso tenha alguma dúvida sinta-se à vontade para perguntar. Após a entrevista permaneceremos disponíveis para qualquer questão que possa surgir.

Consentimento

Fui convidado(a) a participar no estudo sobre "A Crise em Saúde Pública Americana do Opióide sob uma Perspetiva Normativa: Lições para Portugal". Li as informações acima e tive a oportunidade de esclarecer as minhas dúvidas. Aceito voluntariamente participar neste estudo e consinto a gravação na minha entrevista.

Nome do/a Participante:

Assinatura:

Data:

Expliquei detalhadamente as informações deste documento ao/à participante e certifiquei-me de que o/a mesmo(a) entendeu que uma entrevista gravada será realizada. Eu confirmo que o/a participante teve a oportunidade de fazer perguntas sobre o estudo, e que todas as perguntas foram respondidas. Confirmo que o consentimento foi dado voluntariamente.

Uma cópia do consentimento foi disponibilizada ao participante.

Nome e assinatura da investigadora:

Data: